DOPPLER AND PLACENTAL HISTOPATHOLOGY IN PREGNANCIES COMPLICATED BY INTRA UTERINE GROWTH RETARDATION

DISSERTATION SUBMITTED IN FULFILLMENT OF THE REGULATIONS FOR THE AWARD OF M.D. (OBSTETRICS AND GYNAECOLOGY)

DIVISION OF OBSTETRICS AND GYNAECOLOGY

PSG INSTITUTE OF MEDICAL SCIENCES AND RESEARCH

THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY

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CORRELATION STUDY BETWEEN UMBILICAL ARTERY DOPPLER AND PLACENTAL HISTOPATHOLOGY IN PREGNANCIES COMPLICATED BY INTRA UTERINE GROWTH RETARDATION

DISSERTATION SUBMITTED IN FULFILLMENT OF THE REGULATIONS FOR THE AWARD OF M.D. (OBSTETRICS AND GYNAECOLOGY)

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CERTIFICATE

This is to certify that the thesis "**CORRELATION STUDY BETWEEN UMBILICAL ARTERY DOPPLER AND PLACENTAL HISTOPATHOLOGY IN PREGNANCIES COMPLICATED BY INTRA UTERINE GROWTH RETARDATION"** is a bonafide work of **Dr. R. RAJ NAVITHA** done under my direct guidance and supervision in the department of Obstetrics and Gynaecology, PSG Institute of Medical Sciences and Research, Coimbatore in fulfillment of the regulations of The Tamilnadu Dr. M.G.R Medical University for the award of M.D. degree in Obstetrics and Gynaecology.

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CONTENTS

LIST OF ABBREVIATIONS

IUGR	:	Intra uterine growth retardation
FGR	:	Fetal growth retardation
H/A	:	Head to abdomen ratio
F/A	:	Femur to abdomen ratio
AC	:	Abdominal circumference
HC	:	Head circumference
FL	:	Femur length
AFV	:	Amniotic fluid volume
PFGR	:	Pathological fetal growth retardation
AEDV	:	Absent end diastolic velocity
REDV	:	Reduced end diastolic velocity
CLD	:	Chronic lung disease
IVH	:	Intra ventricular hemorrhage

INTRODUCTION

Fetal growth and development remains one of the most complex and fascinating biologic processes known. The fetus has been described as the perfect parasite. Under ideal conditions sufficient amounts of maternal nutrients are provided across a uteroplacental circulation that functions efficiently to meet the demands of the growing fetus. An appropriate hormonal and endocrine milieu for both the mother and the fetus enables optimal growth. This process is dependent on the balanced interactions of many factors. It allows normal development and maturation and ultimately a smooth transition form to extra uterine life. Metabolic shifts occur in virtually all maternal nutrients during pregnancy and the placenta and uteroplacental blood flow plays a key role in the regulation and delivery of these fuels to the fetus.

As gestation advances, a progressive increase in uteroplacental perfusion occurs. A persistently larger fraction of the already augmented maternal cardiac output is directed to the uteroplacental circulation. The increase in uterine blood flow parallels the increase in fetal weight as pregnancy progresses.

If the balance interaction between the mother and the fetus is disturbed it leads to intrauterine growth restriction. Neonates weighing below the 10th percentile for their gestational age are said to have intrauterine growth restriction. It is associated with high perinatal morbidity and mortality as the fetus with intrauterine growth restriction tolerates labour poorly and antenatal diagnosis of intrauterine growth restriction is of great importance. In such

foetuses there is a significant alteration in the rate of blood flow and it acts as a rate limiting factor for oxygen and glucose consumption .

There are various methods to diagnose intrauterine growth restriction. Clinical screening by fundal height measurement and maternal weight gain are used regularly during prenatal care but are affected significantly by extremes of amniotic fluid volume and maternal body habitus.

Ultrasound can also be used to diagnose intra uterine growth restriction. The various parameters used are Biparietal diameter, Head circumference, abdominal circumference, Transverse cerebellar diameter and sonographic estimated fetal weight.

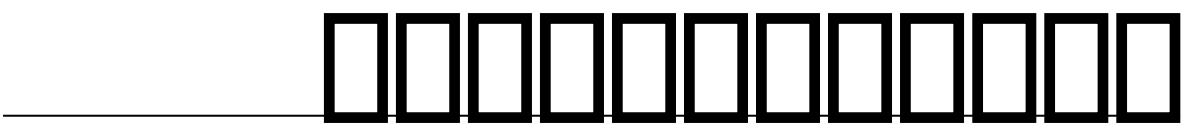
Successful human placentation, resulting in the birth of a healthy infant at term, is dependent upon normal placental development. Uteroplacental bed perfusion increases in normal pregnancy and decrease in intra uterine growth restriction and pregnancy induced hypertension. The alteration in the uterine and umbilical circulation precedes the onset of intrauterine growth restriction. Most cases of growth retardation are hemodynamically mediated at some point making Doppler technology the ideal diagnostic tool for this major perinatal problem.

Foetuses with abnormal flow velocity waveforms have a higher incidence of perinatal asphyxia and death than those with normal flow characterization. Thus Doppler evaluation of the uterine and umbilical blood flow can be used to detect fetal jeopardy in fetus at risk for placental insufficiency. The placental villous dysfunction in growth restricted foetuses with abnormally low umbilical artery blood flow, indicated by absent or reverse end diastolic flow, is characterised by reduced

elaboration of gas-exchanging peripheral villi, which increase the risk of chronic fetal hypoxia and acidosis. Among the large number of maternal factors, maternal hypertension is one of the most important factors in intrauterine growth retardation. Pregnancy induced hypertension associated placental pathology include infarcts, retroplacental haemorrhage, accelerated maturation, fibromuscular hyperplasia and obliterative end arteritis of the fetal stem artery, villous edema, stromal fibrosis, increased number of syncytial knots, cytotrophoblast hyperplasia, trophoblast basement membrane thickening, deficiency of the vasculo syncytial membrane, excessive fibrinoid necrosis, and acute atherosis in decidual vessels.

The known placental pathology of an IUGR infant includes decrease of placental growth, maternal vasculopathy, chronic villitis, increase perivillous fibrin, fetal thrombotic arteriopathy and avascular villi as its secondary feature, umbilical cord anomaly, infarct, cytotrophoblast hyperplasia, basement membrane thickening, etc. Histologic examination of the placentas from IUGR fetuses can supplement clinical knowledge of the cause of IUGR. The present study was undertaken to investigate the pathologic findings regarding the placentas in IUGR foetuses and to correlate the results with Doppler findings.

As with many maternal and fetal conditions, careful evaluation of the placenta may aid in diagnosis of an underlying condition, a recurrent condition, chromosomal abnormalities, or systemic diseases. Only through the careful gross and microscopic pathologic examination of the placenta can an undiagnosed or suspected condition be identified or confirmed.



REVIEW OF LITERATURE

INTRAUTERINE GROWTH RETARDATION:

Normal fetal growth involves hyperplasia and hypertrophy on a cellular level. Disturbance of fetal growth dynamics can lead to reduced cell number, cell size, or both, ultimately resulting in abnormal weight, body mass, or body proportion at birth. Neonates weighing below the 10th percentile for their gestational age are said to have intrauterine growth restriction[1]. Next to prematurity, IUGR is the second leading cause of perinatal mortality[2]. Compared with appropriately grown counterparts, perinatal mortality rates in growth restricted neonates are 6 to 10 times greater; perinatal mortality rates as high as 120 per 1,000 for all cases of IUGR and 80 per 1,000 after exclusion of anomalous infants have been reported[3]. In its most severe form the abnormal umbilical artery Doppler waveform is characterized by absent or reversed end-diastolic flow velocity, and perinatal mortality in this group of pregnancies complicated by intrauterine growth restriction (IUGR) ranges between 40% and 70%[4]. Incidence of IUGR is close to 10% of all births.

CLASSIFICATION OF IUGR:

I. BASED ON PRESENCE OR ABSENCE OF SYMMETRY:

B. Type I / Symmetric FGR: foetuses that are symmetrically small and have normal H/A and F/A ratios

C. Type II / Asymmetric FGR: foetuses that have an AC that is smaller than HC and FL resulting in abnormally high H/A and F/A ratios

D. Type III / Intermediate FGR: foetuses that are initially symmetric but become asymmetric later in the pregnancy

II. BASED ON ORIGIN OF THE PROBLEM:

A. Intrinsic: foetuses those are small due to fetal conditions such as viral infections or chromosomal abnormalities.

B. Extrinsic: growth failure is due to an element outside the fetus such as placental conditions or maternal diseases.

C. Combined: FGR occurs when there are extrinsic and intrinsic factors causing growth failure.

D. Idiopathic: FGR occurs when the cause of fetal growth failure is unknown.

III. ETIOLOGIES OF INTRAUTERINE GROWTH RESTRICTION[5]:

A. Maternal: cardio respiratory diseases, renal diseases, anaemia, acidosis, fever, drugs (diethylstilbestrol, anticancer drugs agents, narcotics), smoking, alcohol.

B. Fetal: Infections, heart disease, malformations, chromosomal abnormalities, osteogenesis imperfecta.

C. Placental: abruptio placentae, placenta previa, thrombosis, infarction, deciduitis, placentitis, vasculitis, edema, chorioamnionitis, placental cyst, chorangioma.

D. Uterine: decreased uteroplacental blood flow, atheromatosis, arteriosclerosis of decidual spiral arteries, connective tissue disorders, chronic hypertension, preeclampsia, diabetes mellitus, fibromyoma, morphologic abnormalities.

REGULATION OF FETAL GROWTH

Fetal growth is regulated at multiple levels and requires successful development of the placental interface between maternal and fetal compartments. In the early first trimester, anchoring villi originating from the cytotrophoblast connect the decidua to the uterus and thereby establish placental adherence. This allows

formation of vascular connections between the maternal circulation and the intervillous space so that increasing quantities of placental secretory products can reach the maternal circulation.

The villous trophoblast now becomes the primary placental site of maternal-fetal exchange. By 16 weeks gestation, the maternal microvillous and fetal basal layer are only 4 microns apart, posing little resistance to passive diffusion. Elaboration of active transport mechanisms for three major nutrient classes (glucose, amino acids, and free fatty acids) and an increase in the villous surface area raise the capacity and efficiency of active transplacental transport. Extravillous cytotrophoblast invasion of the maternal spiral arteries results in progressive loss of the musculoelastic media, a process paralleled on the fetal side by continuous villous vascular branching. This results in significant reduction of blood flow resistance in the uterine and umbilical vessels, converting both circulations into low-resistance, high-capacitance vascular beds. The decrease in vascular resistance is related to two waves of angiogenesis within the placenta. The first is branching angiogenesis occurring at the end of the first and beginning of the second trimester, which increases the number of vascular branches. The second wave is nonbranching angiogenesis, which does not create additional branches but rather results in elongation of the existing placental vascular tree. This latter process occurs at the end of the second and beginning of the third trimester[6].

Owing to these developments, a minimum of 600 ml/min of the maternal cardiac output reaches a placental exchange area of up to $12m^2$ at term[1]. In the fetal compartment, this is matched with a blood flow volume of 200 to 300 ml/kg/min throughout gestation. This magnitude of maternal blood flow is necessary to ensure

maintenance of placental function that is energy intensive and consumes as much as 40 percent of the oxygen and 70 percent of the glucose supplied. Optimal fetal growth and development depends on a magnitude of maternal nutrient and oxygen delivery to the uterus that leaves sufficient surplus for fetal substrate utilization.

PATHOPHYSIOLOGICAL CHANGES IN IUGR:

Maternal Impacts

Placental dysfunction affects several aspects of maternal adaptation to pregnancy. When trophoblast invasion remains confined to the decidual portion of the myometrium, maternal spiral and radial arteries fail to undergo the physiologic transformation into low resistance vessels, which is generally expected by 22 to 24 weeks[7,8]. Normal and abnormal spiral artery adaptation can be detected with maternal uterine artery Doppler studies. Maternal placental floor infarcts, fetal villous obliteration, and fibrosis increase placental blood flow resistance, producing maternal-fetal placental perfusion mismatch that decreases the effective exchange area[9]. With progressive vascular occlusion, fetoplacental flow resistance is increased throughout the vascular bed and eventually metabolically active placental mass is reduced.

Fetal Impacts:

Metabolic manifestations occur early in growth-restricted fetuses. With progression of placental insufficiency, nutrient deficits become universal and result in decreased fetal and placental size. When uterine oxygen delivery falls below a critical value (0.6 mmol/min/Kg fetal body weight in sheep), fetal oxygenation begins to fall and is eventually accompanied by fetal hypoglycaemia[10]. The initially mild hypoglycaemia results in a blunted fetal pancreatic insulin response, allowing

glycogenolysis from hepatic glycogen stores[11]. The minimal hepatic glycogen stores in the fetus are quickly depleted as glucose and lactate are preferentially diverted to the placenta. An increasing metabolic manifestations occur early in growth-restricted fetuses. With progression of placental insufficiency, nutrient deficits become universal and result in decreased fetal and placental size. When uterine oxygen delivery falls below a critical value (0.6 mmol/min/Kg fetal body weight in sheep), fetal oxygenation begins to fall and is eventually accompanied by fetal hypoglycaemia[10]. The initially mild hypoglycaemia results in a blunted fetal pancreatic insulin response, allowing glycogenolysis from hepatic glycogen stores[11].

The minimal hepatic glycogen stores in the fetus are quickly depleted as glucose and lactate are preferentially diverted to the placenta. An increasing nutrient deficit leads to worsening fetal hypoglycaemia. Limitation of amino acid transfer and breakdown of endogenous muscle protein to obtain gluconeogenic amino acids depletes branched-chain and other essential amino acids[12]. Simultaneously, lactate accumulates owing to the limited capacity for oxidative metabolism. Placental transfer of fatty acids loses its selectivity particularly for essential fatty acids. Reduced utilization leads to increased fetal free fatty acid and triglyceride levels with a subsequent failure to accumulate adipose stores. In this setting of advancing malnutrition, cerebral and cardiac metabolism of lactate and ketones is up regulated to remove these accumulating products of anaerobic metabolism[13]. Acid-base balance can be maintained as long as acid production is met by sufficient buffering capacity of fetal haemoglobin and an equal disposition by these organs. Thus, metabolic compromise progresses from simple hypoglycaemia, hypoxemia, and decreased levels of essential amino acids to overt hypo aminoacidemia, hypercapnia,

hypertriglyceridemia, and hyperlacticemia. The lactate production is exponentially correlated to the degree of acidemia that generally results from this metabolic state[14].

Table 1

Metabolic Responses to Placental Insufficiency

SUBSTRATE	CHANGE
Glucose	Decreased proportional to the degree of fetal hypoxemia.
Amino acids	Significant decrease in branched-chain amino acids (valine, leucine, isoleucine) as well as lysine and serine. In contrast, hydroxyproline is elevated. The decrease in essential amino acids is proportional to the degree of hypoxemia. Elevated amniotic fluid glycine-to-valine ratio. Elevations in amniotic fluid ammonia, with a significant positive correlation with the fetal ponderal index.
Fatty acids and triglycerides	• Decrease in long-chain polyunsaturated fatty acids (docosahexanoic and arachidonic acids). Decrease in overall fattya cid transfer only with significant loss of placental substance. • Hypertriglyceridemia due to decreased utilization
Oxygen and CO_2	• Degree of hypoxemia proportional to villous damage and correlates significantly with hypercapnia, acidemia and hypoglycemia and hyperlacticemia.

In growth-restricted fetuses, declining function at all levels of the thyroid axis correlate to the degree of hypoxemia[15]. Thyroid gland dysfunction may develop, as indicated by low levels of thyroxine and triiodothyronine despite elevated thyroid-stimulating hormone levels. In other instances, central underproduction of thyroid-stimulating hormone may be responsible for fetal hypothyroidism[16]. Finally, down regulation of thyroid hormone receptors may limit the biologic activity of circulating thyroid hormones in specific target tissues such as the developing brain[17].

Elevations in serum glucagon, adrenaline, noradrenaline, and stimulation of the fetal glucocorticoid axis have immediate effects in fetal life promoting the mobilization of hepatic glycogen stores and peripheral glycogenolysis[18].

HAEMATOLOGICAL RESPONSE:

Fetal hypoxemia is a trigger for erythropoietin release and stimulation of red blood cell production through both medullary and extramedullary sites resulting in polycythemia[19]. Oxygen-carrying capacity and the buffering capacity are thus increased through the elevation in haemoglobin count. If extramedullary haematopoiesis is increasingly induced by prolonged tissue hypoxemia or acidosis, the nucleated red blood cell count rises owing to the escape of these cells from these sites. In advanced placental insufficiency, more complex hematologic abnormalities supervene that may result from dysfunctional erythropoiesis, placental consumption, and vitamin and iron deficiency[20]. Subsequently, fetal anaemia and thrombocytopenia are observed, particularly in fetuses with marked elevation of placental blood flow resistance and evidence of intraplacental thrombosis suggesting a causative relationship[21,22]. An increase in whole blood viscosity[23], a decrease in red blood cell

membrane fluidity[24], and platelet aggregation may be important precursors for accelerating placental vascular occlusion and dysfunction.

CELLULAR AND HUMORAL LEVEL:

Decreases in immunoglobulin, absolute B-cell counts, total white blood cell counts, neutrophil, monocyte and lymphocyte sub populations, as well as selective suppression of T-helper and cytotoxic T cells are related to the degree of acidemia.

DIAGNOSTIC TOOLS:

Obstetric history: predisposing factors → maternal age <19yrs or >36yrs, grand multiparity, pre-pregnant maternal weight <45kgs, bleeding per vaginum > 28 wks suggestive of placenta previa or abruption, previous history or family history of IUGR[1].

MATERNAL HISTORY:

History suggestive of chronic hypertension, preeclampsia, chronic renal disease, diabetes with vascular involvement, cardiac disease, sickle cell anaemia, smoking, alcohol, living at high altitude predisposes to IUGR[1].

CLINICAL SCREENING:

Poor maternal weight gain: poor maternal weight gain during pregnancy is a relatively insensitive sign of inadequate fetal growth, stationary or falling weight may suggest IUGR.

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Symphyseal fundal height:

The maternal uterine fundus is objectively measured and charted during each antenatal visit. After 20 wks, the normal symphyseal fundal height in centimetres approximates the number of weeks of gestation. Sensitivity for detection of IUGR ranges from 60%-85%, and positive predictive values are 20% to 80%[5].

Abdominal palpation:

Serial clinical examination to measure the relative growth of the uterus and its contents is the mostly used method. The range of error is 2 weeks in the I trimester and 4 weeks in the II and III trimester. Sensitivity is 44%[1].

BIOCHEMICAL SCREENING:

Atleast four hormones or protein markers measured in the maternal sera early in the II trimester are associated with subsequent IUGR. These include estriol, human placental lactogen, hCG, and alpha fetoprotein. Clinically, maternal serum alpha feto protein is the most useful as a marker of abnormal placentation. Most studies conclude that a single, unexplained elevated value increase the risk of growth restriction 5 to 10 fold[5].

UTERINE ARTERY DOPPLER STUDIES

An early diastolic notch in the uterine arteries at 12 to 14 weeks suggests delayed trophoblast invasion, whereas persistence of "notching" beyond 24 wks provides confirmatory evidence. A uterine artery Doppler resistance profile that is high, persistently notched, or both, identifies women who are at risk for preeclampsia and IUGR. Sensitivity is 85%[5].

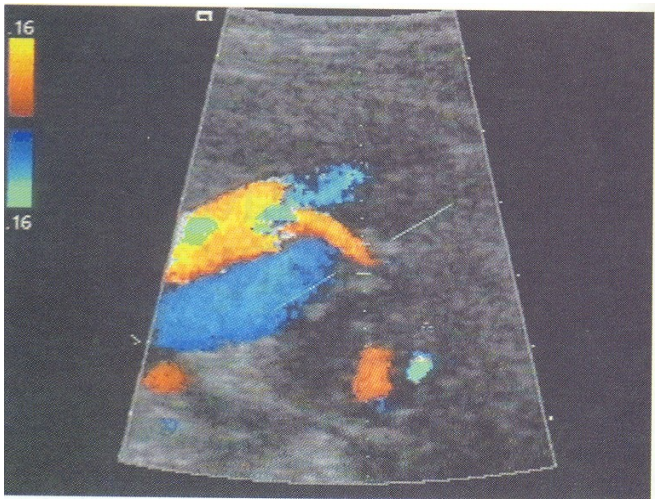


Fig 1: Persistance of early diastolic notch after 24 weeks identifies women at risk of IUGR

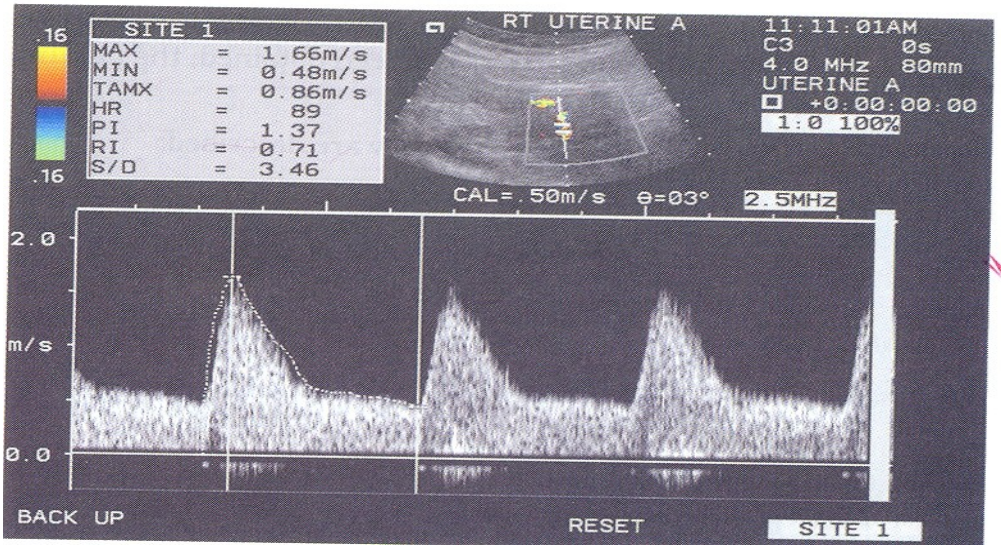


Fig 2 : Uterine Artery Normal

ULTRASONIC DIAGNOSIS:

Ultrasound biometry is the diagnostic tool of choice for documentation of fetal growth disorders. Once the gestational age is assigned, the interpretation of an ultrasound growth study is based upon the fetal anatomic survey, amniotic fluid volume, percentile rank of fetal size measurements, interval growth since the last study, and functional assessment of the placental unit with Doppler ultrasound (umbilical and uterine arteries).

Direct measurements:

Biparietal Diameter:

It's a poor tool for the detection of IUGR. The majority of growth-restricted fetuses presenting with asymmetric growth restriction and delayed flattening of the cranial growth curve would be detected relatively late

Head Circumference:

The HC is not subject to the same extrinsic variability as the BPD. The measurement technique is important because calculated HC measurements are systematically smaller than those directly measured. As a screening tool for IUGR, the HC poses a similar problem because the BPD in that two thirds of IUGR fetuses with asymmetric growth pattern would be detected late.

Abdominal Circumference:

The AC is the single best measurement for the detection of IUGR[25] because it is related to liver size, which is a reflection of fetal glycogen storage. The most accurate AC is the smallest directly measured circumference obtained in a perpendicular plane of the upper abdomen at the level of the hepatic vein between

fetal respirations[26]. Sensitivity is 95% and specificity is 60%.positive predictive value is 21% and negative predictive value is 99%.

Femur Length:

FL is not affected in asymmetric IUGR. Sensitivity is 45% and specificity is 97%.positive predictive value is 64% and negative predictive value is 94%.

Transverse cerebellar Diameter:

It is one of the few soft tissue measurements that correlate well with gestational age[27], being relatively spared from the effects of mild to moderate uteroplacental dysfunction. Whether its measurement offers any advantage over bony measurements in the assessment of compromised fetal growth is controversial[28,29].

Estimated fetal weight:

Ultrasonic fetal weight estimates are usually within 5-10% of the true fetal weight. Sensitivity is 89% and specificity is 88%. Positive predictive value is 45% and negative predictive value is 99% for the detection of FGR (Ott, 1997). The most commonly used formula to determine EFW and the most commonly used percentile distribution nomograms are Hadlock et al (1984, 1991).

Amniotic Fluid Index:

This is measured with a four quadrant technique and is obtained by the sum of four deepest vertical pools in each quadrant. A relationship between oligohydramnios and progressive deterioration of arterial and venous Doppler studies has been documented in growth-restricted fetuses and prolonged pregnancies[30]. Therefore, declining AFV is suggestive of ineffective downstream delivery of cardiac output, allowing some form of longitudinal monitoring even in the absence of Doppler

studies. The regulation of AFV by the late second and third trimester is primarily dependent on fetal urine output, production of pulmonary fluid, and fetal swallowing. Placental dysfunction and fetal hypoxemia both may result in decreased perfusion of the fetal kidneys with subsequent oliguria and decreasing AFV[31]. Its a late sign of IUGR. Sensitivity is 83% and Specificity is 60%.

Table 2
Incidence of IUGR in Oligohydramnios

Vertical pocket	Incidence of IUGR
>2 cm	6%
1- 2 cm	20%
< 1 cm	39%

MEASUREMENT RATIOS:

Head to abdomen ratio (HC/AC):

This ratio compares the most preserved organ in the malnourished fetus, the brain, represented by the circumference of the fetal head, with the most compromised organ, the liver, represented by fetal AC. In a normally growing fetus HC/AC ratio compromised organ, the liver, represented by fetal AC. In a normally growing fetus HC/AC ratio exceeds 1.0 before 32 wks. It is approximately 1.0 at 32-34 wks. After 34 wks it falls below 1.0. If the fetus is affected by asymmetric IUGR, the HC remains larger. The HC/AC ratio is then elevated. In symmetric IUGR both the HC and AC are reduced and the ratio remains normal. Using this HC/AC ratio, 85% of IUGR foetuses are detected[5].

Femur length to abdomen circumference (FL/AC):

This ratio remains constant after 20 wks. The normal value for this index is 22±2. An upper limit of 23.5 has a sensitivity of 63.3% and a specificity of 90% for the diagnosis of FGR.

Fetal ponderal index (FPI):

FPI is gestational age independent and has a constant value throughout the second half of pregnancy. It is obtained by dividing the EFW by the third power of FL (vintzileos et al., 1986). Its normal value is 8.325 ± 2.5 (2 SD).An FPI of 7.0 / less should be considered abnormal and suggestive of PFGR. Sensitivity is 55% and specificity is 71%.positive predictive value 18% and negative predictive value is 92%[32].

DOPPLER STUDIES:

The use of Doppler for the evaluation of fetal circulation is based on the principle of change in frequency of a sound wave when it is reflected by a moving object. The role of Doppler velocimetry in the management of fetal growth restriction is unique because it serves as a diagnostic as well as a monitoring tool. Doppler flow velocity waveforms may be obtained from arterial and venous vascular beds in the fetus.

Umbilical artery Doppler:

It's a powerful tool that allows to follow a sequence of fetal hemodynamic events that happens in response to placental insufficiency. Arterial Doppler waveforms provide information on downstream vascular resistance, which may be altered owing to structural changes in the vasculature or regulatory changes in vascular tone.

The systolic/diastolic ratio, resistance index, and the pulsatility index are the three Doppler indices most widely used to analyze arterial blood flow resistance. An increase in blood flow resistance manifests itself with a relative decrease in end-diastolic velocity resulting in an increase in all three Doppler indices. Of these indices, the pulsatility index has the smallest measurement error and narrower reference limits. With extreme increase in blood flow resistance, end-diastolic forward velocity may be absent (AEDV) or reversed (REDV)[32].

Table 3
Arterial Doppler Indices

ARTERIAL DOPPLER INDICES	CALCULATION
S/D ratio	$\frac{\text{systolic peak velocity}}{\text{diastolic peak velocity}}$
Resistance index (RI)	$\frac{\text{systolic - end peak velocity}}{\text{systolic peak velocity}}$
Pulsatility index (PI)	$\frac{\text{systolic - end peak velocity}}{\text{time averaged maximum velocity}}$

Factors affecting the umbilical artery Doppler waveform in a normal pregnancy:

1. State of pregnancy:

It is influenced by gestational age with advancement of pregnancy, the end-diastolic velocity increases and the S/D ratio declines progressively.

2. Fetal heart rate:

With bradycardia, the diastolic phase increases and the end- diastolic velocity decreases and thereby a increase in the S/D ratio, pulsatility index and resistance index. Converse changes occur with tachycardia.

3. Fetal breathing:

Doppler indices should be measured only during fetal apnea, because when the fetus breathes there are appreciable changes in the intrathoracic and central circulatory dynamics, which is associated with changes in the peak systolic and end -diastolic components of the maximum frequency shift from one cardiac cycle to the next.

4. Site of Doppler sampling in the cord:

A free umbilical cord loop which is floating in amniotic fluid is examined with continuous or pulsed Doppler ultrasound far from the fetal and placental insertions (e.g., midcord segment) .If the sample is taken near the placental site lower S/D ratios are obtained and the highest S/D ratios are obtained if it is taken near the fetal abdominal wall.

Normal values of S/D ratio is as follows: At 20 wks → it is 7.5, at 28 wks → it is 5, at 34 wks it is 3.6 , at 38 wks it is 3.0, at 40 wks it is 2.8. RI > 0.72 abnormal. Umbilical artery doppler-sensitivity: 78% and specificity: 87% [5].

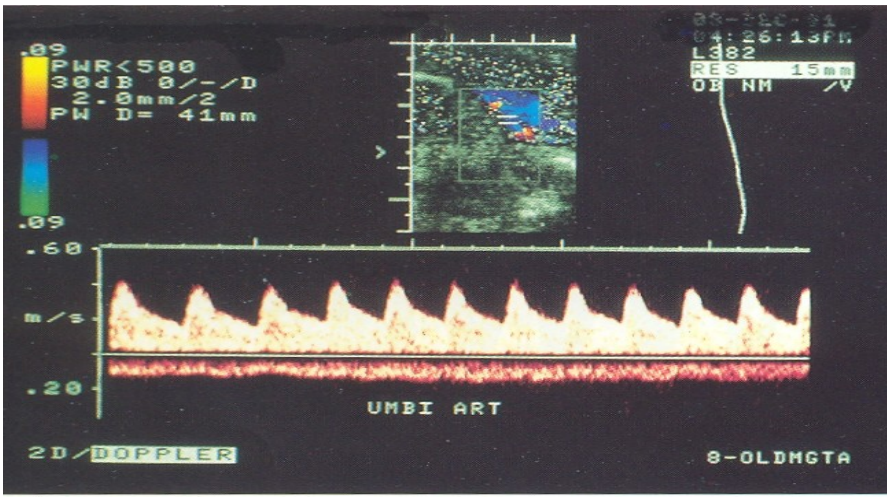


Fig 3 : Normal end diastolic flow

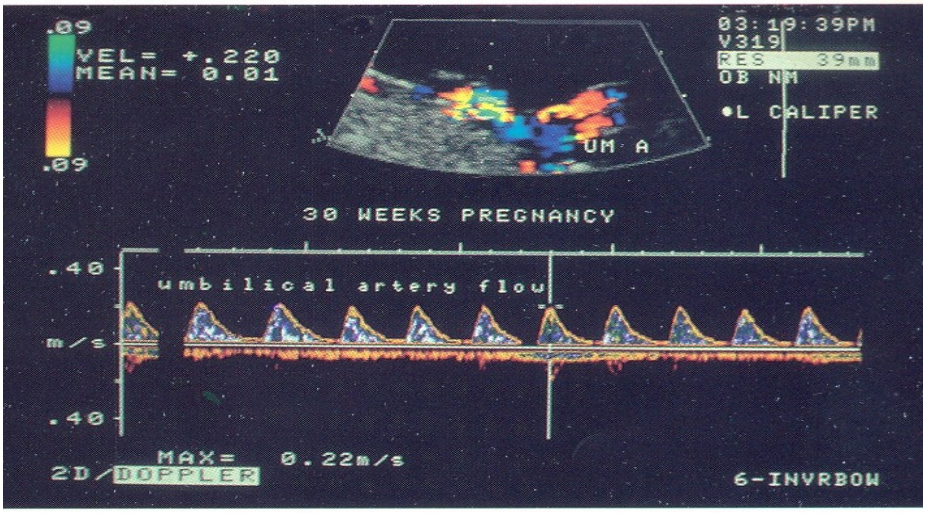


Fig 4: Absent end diastolic flow

In 1983, a study by campell et al[34] was the first to demonstrate a correlation between pregnancies complicated by hypertension and IUGR and decreased end diastolic velocities in the arcuate arteries . This finding was associated with low birth weight , fetal distress, low apgar scores and an increased caesarean section rate. Furthermore, proteinuria and severe hypertension correlated significantly with abnormal Doppler indices. Rochelson et al[35] studied the extreme umbilical flow waveform abnormalities of absent or reversed diastolic flow and was the first to report 8 perinatal deaths among 15 fetuses with absent end diastolic flow. However this series had also included foetuses with congenital anomalies.

Milder forms of placental vascular dysfunction, especially near term, may not produce elevation of umbilical artery blood flow resistance sufficiently to be detectable by traditional Doppler methods. If placental gas exchange is sufficiently impaired to result in perceived fetal hypoxemia, a decrease in middle cerebral artery Doppler resistance may occur . Another Doppler index frequently used clinically to detect this condition is the ratio between umbilical artery pulsatility as index of

vasoconstriction in the placenta and middle cerebral artery pulsatility as index of vasodilation in the fetal brain. In milder forms of placental disease with near-minimal increase in umbilical artery blood flow resistance the cerebroplacental Doppler ratio (CPR) may decrease. For the umbilical artery, an abnormal test result is defined as a Doppler index measurement of greater than 2 SDs above the gestational age mean and/or a loss of end-diastolic velocity. Like growth curves, it is best to use nomograms developed from a local or comparable population. For the CPR and also for the middle cerebral artery, a greater than 2 SD decrease of the index is considered abnormal. In a setting of small fetal size, these findings identify those fetuses at greatest risk for adverse outcome.

Bras and Platt in 1988 and Lingman et al in[36] confirmed the association of absent end diastolic flow with adverse fetal outcome. There was 50% mortality among 12 Patients with extreme abnormal waveforms.

A reduction of umbilical venous blood flow volume may be the earliest Doppler sign of subtle decrease in fetal villous perfusion[32] umbilical artery waveforms correlate with both the tertiary villous architecture and blood flow resistance. At least 30% of the fetal villous vasculature is abnormal when the umbilical artery end diastolic velocities are low and resistance indices are elevated. Absence or reversal of umbilical artery end-diastolic velocities suggests that 60% to 70% fetal villous vasculature is affected[33].

Placental respiratory function is related to the integrity of the villous vasculature and a decrease in arterial PO_2 can trigger autoregulatory adjustments of vascular smooth muscle tone. As diagnostic tools, elevated umbilical artery blood flow resistance and middle cerebral artery brain sparing provide evidence of placental dysfunction.

Table 4

Summary of Vascular Responses in Fetuses with IUGR[37]

DOPPLER FINDING	PHYSIOLOGIC SIGNIFICANCE
Uterine artery notching	Trophoblast invasion remains limited to the myometrial portion of the spiral arteries. Subsequent failure to fully transform into a low resistance, high capacitance vascular bed increases risk for subsequent IUGR or preeclampsia
Decreased, absent, or reversed umbilical artery end-diastolic velocity	Abnormal terminal villi and stem arteries result in increased placental vascular resistance and a proportional decrease in the umbilical artery end-diastolic velocity. Associated placental perfusion defects are responsible for impaired feto-maternal gas and nutrient exchange.

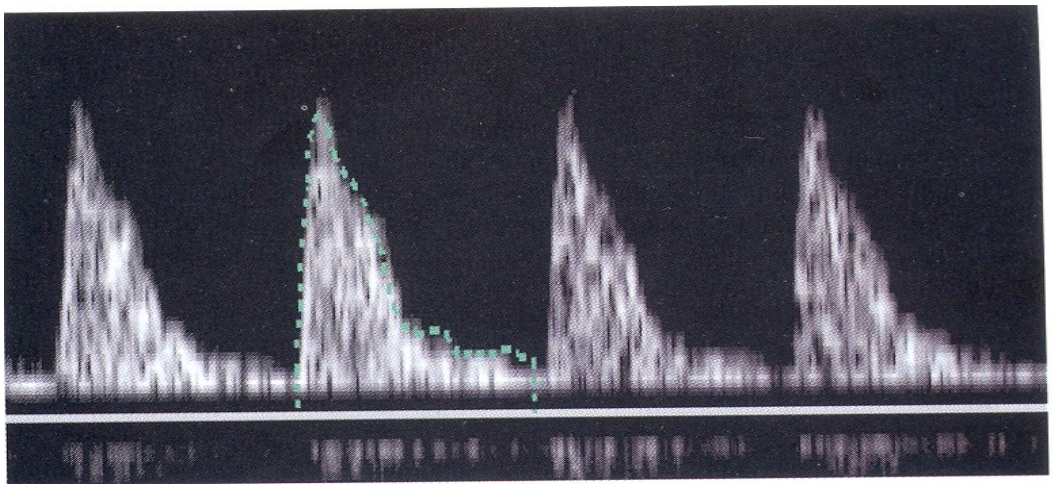


Fig 5: Middle cerebral artery-normal

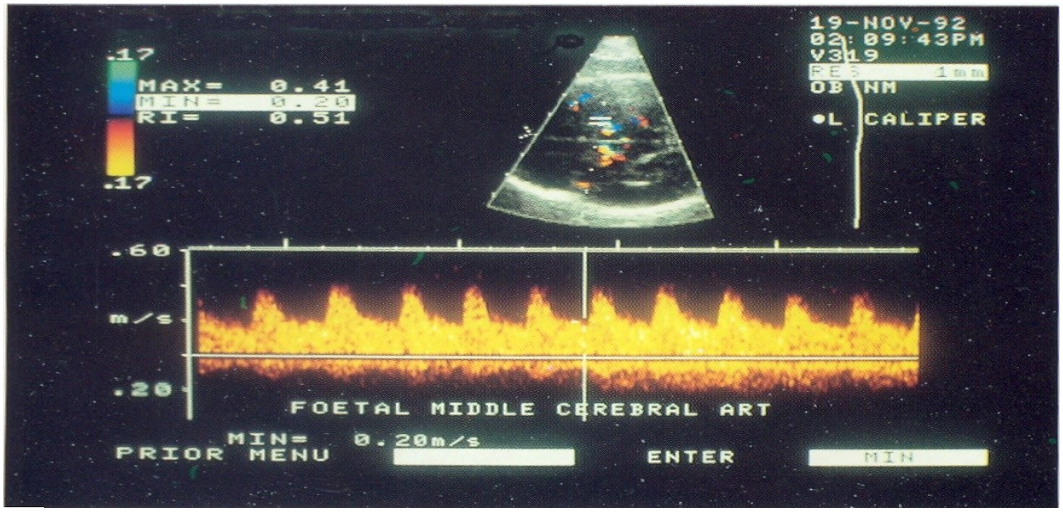
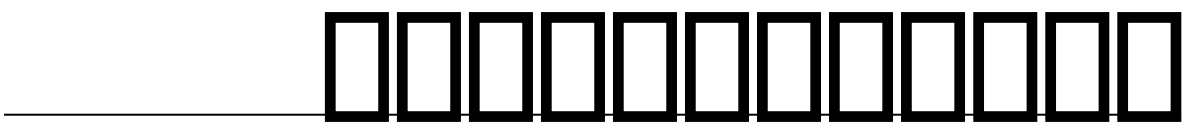


Fig 6: Increased End Diastolic Flow- Brain Sparing Effect



THE PLACENTA

The placenta is a temporary organ required for the development of the embryo and fetus. It allows for the exchange of metabolic products between the fetus and the mother.

Placental Functions

The placenta functions in metabolism, in the transport of substances and in endocrine secretion.

Metabolism:

During early pregnancy, the placenta synthesizes glycogen, cholesterol and fatty acids, which serve as sources of nutrients and energy for the embryo and fetus.

Transport:

The placenta has a very large surface area, which facilitates the transport of substances in both directions. The surface area at 28 weeks is 5 square metres, and at term it is almost 11 square metres. About 5 to 10% of this surface area is extremely thin, measuring only a few microns.

The bulk of the substances transferred from mother to fetus consists of oxygen and nutrients. The fetus eliminates carbon dioxide and waste materials (eg., urea and bilirubin) into the maternal circulation.

The exchange of gases occurs via diffusion. The placenta is also highly permeable to glucose, but much less permeable to fructose and other common disaccharides. Amino acids are transported through specfic receptors. Some proteins

are transferred slowly through the placenta, mainly via pinocytosis. The transfer of maternal antibodies (mainly IgG) is important in providing passive immunity to the newborn. Another maternal protein, transferrin, carries iron to the placental surface, from there it is actively transported into the fetal tissues. Steroid hormones easily cross the placental barrier; protein hormones are much more poorly transported (but maternal thyroid hormone gains slow access to the fetus, and fetal insulin can reduce symptoms of maternal diabetes). The placenta is also very permeable to alcohol and other drugs and to some viruses.

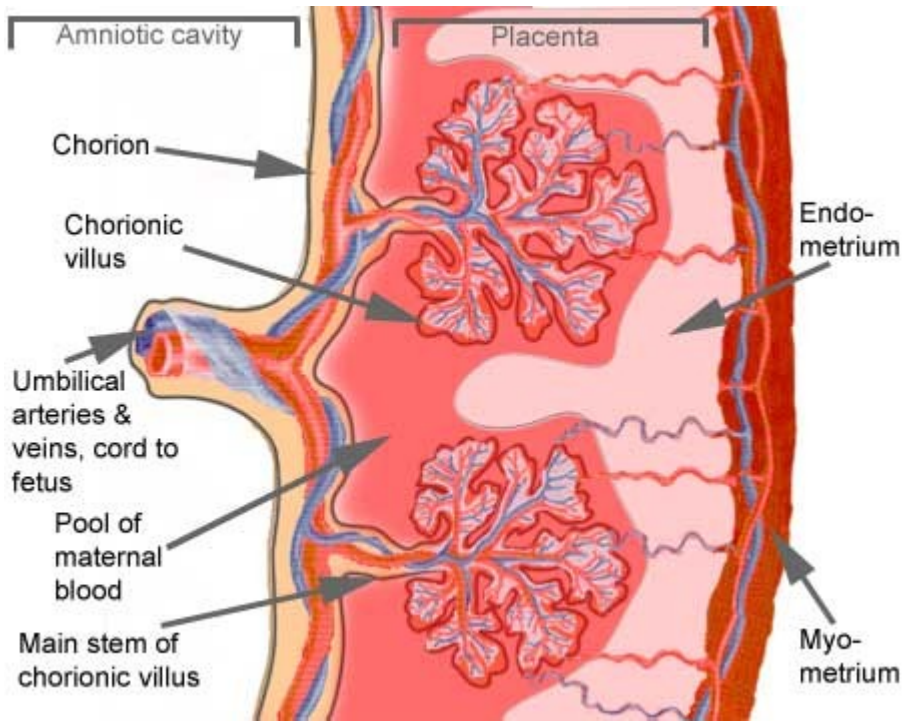


Fig 7: Cross Section view of Placenta

At the end of the pregnancy six types of villi are to be found in the placenta:

1. Stem villi
2. Tertiary mesenchymatous villi
3. Immature intermediate villi
4. Mature intermediate villi

5. Terminal or free villi
6. Trophoblast buds

An oxygen tension exists between maternal deciduas and villous placenta during embryonic development[39]. The stem villi guarantee the mechanical stability of the villus tree, the immature intermediate villi are the place of the proliferation of the trophoblast and the trophoblast buds. Tertiary villi (mesenchymatous) are responsible for the lengthening of the villus tree.

From the mature intermediate villi the free villi or terminal villi arise which makes up 40% of the volume and 50% of the exchange surface of the placenta before birth. Extravillous trophoblast proliferates within "hypoxic" cell columns before invading the uterine stroma and the spiral arterioles[39].

During embryogenesis the villi are mainly mesenchymal, differentiating towards immature intermediate villi (Castellucci et al., 1990). They are poorly vascularised structures, resulting in high fetoplacental vascular impedence: the corresponding umbilical artery waveform is charecterized by AEDFV[39].

Histopathological changes:

In 1995 Carolyn M. Salafia ,Victoria K. Minior [38] studied IUGR in infants less than 32 wks and associated pathologic features. He studied maternal and neonatal charts and placental tissues from 420 consecutive non-anomalous live born infants delivered at <32 wks . He observed that a greater proportion of cases with IUGR had lesions of uteroplacental insufficiency or chronic viilitis than did appropriately grown preterm infants. The statistical relationship of most placental lesions to IUGR depends on the presense or absence of preeclampsia.

In 1999 Tullia Todros[40] examined 18 placentas from IUGR, preterm pregnancies with pre eclampsia, 10 cases with positive end diastolic flow and eight with absent diastolic flow and compared with 6 gestational age matched controls. sections of villous placenta were examined.He found that compared with absent / reverse diastolic flow, the placentas from the positive end diastolic flow showed a normal pattern of stem artery development, accompanied by increased capillary angiogenesis and terminal villous development. These features are suggests an adaptive pathway for the placenta in the fase of uteroplacental ischemia.

Gross abnormalities associated with growth restriction[42]:

R Weslie Tyson (2008) studied about the gross abnormalities in IUGR which includes decreased placental weight as compared with expected for gestational age, evidence of subacute to chronic abruption including villous infarction, decidual necrosis, and staining of fetal membranes by hemosiderin; large space occupying lesions that may include villous infarctions, but also increased deposition of intervillous fibrinoid, areas of unusual paleness that often representing loss of fetal vascularisation of chorionic villi, and less frequently tumour masses. The latter lesions are most commonly represented by chorangiomas but can include abnormalities of villous development, such as hydropic change, mesanchymal dysplasia, and rarely metastatic fetal and maternal neoplasms[38].

Histologic abnormalities associated with growth restriction:

The functional unit of human placenta, the chorionic villus, goes through a developmental process beginning very early after conception and likely continues to some degree up until detachment from the uterine wall. In essence, this process takes large, poorly vascularised chorionic villi with two layers of trophoblastic elements

through a process of branching and vascular proliferation that later in gestation ends with small chorionic villi that are well vascularised with five to eight fetal capillaries in close approximation to the maternal blood in the intervillous space. In the mid to late third trimester, the separation of fetal and placental blood is only by a thin fused basement membrane called the vasculosyncitial membrane.

A study was undertaken at Department of pathology, Samsung cheil hospital, korea-clinicopathologic findings in which 45 cases with IUGR were reviewed, and they were compared with 24 normal control cases. The IUGR groups had significantly shorter mean gestational ages, lower mean placental weights, and higher incidence of ol;igohydramnios, compared to normal controls ($P < 0.05$). Histologically, IUGR was characterised by increased incidence of decidual vasculopathy (31.1%), multiple and severe infarct ($P < 0.05$), villous fibrosis(31.1%), syncytiotrophoblastic knots (86.7%), and higher degree of increased perivillous fibrin deposition ($P < 0.05$). however, there were no statistically significant difference in the placental lesions between hypertensive and normotensive IUGR cases, except for decidual vasculopathy[41].

Table 5

Maternal conditions associated with growth restriction[41,42,43]
R Weslie Tyson (2008)

Maternal conditions	Gross findings	Microscopic findings
Hypertensive states	Small placenta with villous infarction +/- evidence of abruption	Villous ischaemic changes
Diabetes mellitus	Large, boggy placenta but may be small due to poor diabetic control	Irregular villous maturation with hypervascularity / chorangiosis
Hypercoagulable states	Small placenta, evidence of abruption,villous infarctions	Thrombi / vasculopathic change within uteroplacental vessels, villous infarction
Substance abuse	Evidence of abruption	Variable with irregular villous development and villous infarction, +/- evidence of abruption
Sickle cell disease	Small placenta	Villous ischaemic changes with sickle cells in intervillous space
High altitude pregnancies	Variably sized placenta	Hypervascular chorionic villi/chorangiosis, ischaemic changes

Abnormalities of umbilical cord: It is associated with growth restriction may be represented at gross level either by marginal or membranous insertion of the cord. At both the gross and microscopic level it is important to sample the intermembranous or near membranous vessels to evaluate for the presence of organising thrombi. Additionally the umbilical cord can show abnormal tight twisting or constrictions, again leading to decreased placental-fetal exchange leading to growth restriction. Umbilical cord coiling index[46] has been proposed as cords which are hypercoiled can be associated with IUGR, meconium, and fetal distress[43]. Careful gross evaluation and selected sampling of fetal surface vessels may show obstruction at a more distal level with organising fibrin thrombi in the fetal surface vessel or primary branches,and /or hemorrhagic endovasculopathy.

Histologic evaluation of fetal membranes: R Weslie Tyson et al.,[42] (2008) studied this and showed the following

a. presence of meconium → indication of acute/ subacute / chronic stress
b. presence of hemosiderin → evidence of abruption
c. maternal lymphocytic infiltrate seen at the decidual or chorionic interface, gives a clue for non specific villitis
d. fetal membranes usually have associated maternal decidua which allows for the evaluation of the modified spiral arterioles - abnormalities include muscularised vessel wall, presence of fibrinoid necrosis with the presence of macrophages → seen in hypertensive states, collagen vascular diseases, lupus anticoagulant syndrome, and other maternal systemic illness.

Histologic evaluation of fetal surface of placenta:

Macara et al 45 worked on the structural analysis of placental terminal villi from IUGR with abnormal umbilical artery Doppler waveforms. They foundthat the terminal villi from IUGR cases were smaller in diameter than those controls, and had increased syncytial nuclei, reduced cytotrophoblastic nuclei, thickened basal lamina, and increased stromal deposition of collagen and laminins.the observed major findings in IUGR group were presence of decidual vasculopathy, infarct, increased ST knots, villous fibrosis, extensive perivillous fibrin deposition.

R Weslie Tyson (2008) his study suggests to look for vascular abnormalities such as organising thrombi and lesions of hemorrhagic endovasculopathy, evidence of hemosiderin deposition, chronic inflammation at chorionic plate, and localised / diffuse fibrinoid deposition.

Histologic evaluation of maternal surface of placenta:

R Weslie Tyson et al., (2008) evaluated the uteroplacental vessels for the above lesions, and addiionaly there was evidence of decidual necrosis, adherent blood clots, and associated villous infarction which is supportive of subacute / chronic abruption.

Histologic evaluation of chorionic villi[47]

R Weslie Tyson et al., (2008) showed that gestational age will alter the chorionic villus morphology. He proved that increased vascularisation is supportive of chronic low grade underperfusion state. The finding of mononuclear inflammation by maternally derived T cells is felt to be due to maternal-fetal tissue interaction and can recur in subsequent pregnancy in a more fulminant fashion.

Villitis can be associated with intervillositis and massive intervillous fibrin deposition.

Table 6

Fetal and placental histologic abnormalities with growth restriction[42]:

Maternal conditions	Gross findings	Microscopic findings
Chromosomal	Small / boggy placenta	Variable villous morphology with edema, basement membrane mineralisation, and increased villous scalloping
Infections	Variable	Variable
Monochorionic multiple gestations	Sharing of placental vasculature	Variable congestion and edema
Dichorionic multiple gestations	Dichorionic placentation with asymmetrical division of placental volume	Variable with regions of villous ischemia and /or irregular villous maturation
Massive intervillous fibrin deposition	Variable sized placenta with homogenous tan parenchymal appearance	Increased peri and intervillous fibrinoid deposition surrounding largely viable chorionic villi
Chronic villitis	Variable sized placenta	Mononuclear inflammation of chorionic villi
Intervillositis	Variable sized placenta	Increased immature mononuclear cells within intervillous space

Macara L. etal[45] proved that the defect in fetoplacental vascular perfusion represented by absent end-diastolic flow velocity is associated with chronic fetal hypoxia, hypercapnia, and acidosis, indicating a major defect in transplacental gas exchange[45]. These observations have led to the assumption that the placenta (to be precise, the intervillous space and peripheral villous tree) is similarly hypoxic because uteroplacental blood flow is reduced[46].

The appropriate response of the terminal villous network to intervillous space hypoxia (for example, with maternal anemia or gestation at high altitude) is an increase in capillarization of the terminal villi and a reduction in diffusion distance[47].

Recorded variables from gross placental examination included umbilical cordlength,insertion, vessel number, and placental weight, from which the fetoplacental index (birth weight/placental weight[49] was computed. Pathological features were divided into seven types: (1) ischemic changes such as hemorrhagic endovasculitis (HEV), perivillous fibrin deposition, villous ischemia and hemorrhage, and chorangiosis; (2) villous infarction and decidual necrosis; (3) chronic villitis; (4) abnormal villus maturity (delayed, advanced, variable, and dysmaturity); (5) placental abruption; (6) meconium staining; and (7) others, such as villous edema, intervillous thrombosis, amnion nodosum, and congested villi, after Beebe et al[49]. The pathologies were noted as present or absent, and no attempt was made to quantify the extent of the lesions. Pathological definitions were based on the guidelines published by the College of American Pathologists[50]. The data specifically examining chorioamnionitis and neonatal outcomes have been published previously.

Placental Pathology and IUGR

Our data support a role for placental abnormalities in the development of intrauterine growth restriction (IUGR)[51-54], and suggest the convergence of at least two pathologic developmental pathways leading to IUGR, presumably through placental insufficiency. One of these pathways probably involves placental ischemia and placental infarction, leading to decreased placental perfusion. Changes associated with decreased placental perfusion such as ischemic changes and those related to maternal thromboembolic events have been reported before in association with growth restriction[53,54]. Many of these changes are also associated with maternal hypertension, and it is likely that hypertensive disorders of pregnancy are associated with this pathway to IUGR[54]. Changes of this nature are seen most frequently in fetuses with IUGR who show abnormalities in umbilical artery Doppler measurements[55].

Whether villous maturation abnormalities are the result of a decrease in placental perfusion or somehow share in its etiology is not clear, but these abnormalities may be partially explained by the presence of maternal hypertension. An alternative path to placental insufficiency and IUGR may involve chronic villous inflammation. In general, 5% of cases of villitis can be attributed to intrauterine infection, whereas the great majority are classified as villitis of unknown etiology (VUE) [50]. In our population, this pathology was seen most frequently in the placenta of IUGR infants, but this feature was not related to the presence of maternal hypertension, suggesting that this represents an independent path to growth restriction. It may therefore be possible to subclassify and group placental pathologies associated with IUGR infants, as shown in the table.

Table 7

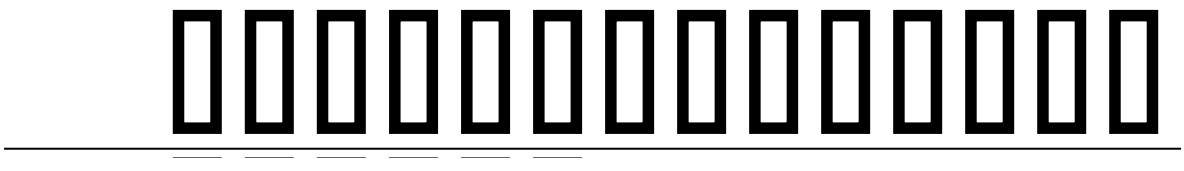
Subclassification of Placental pathologies in IUGR (Beebe et al.,[52])

Subclassification	Placental findings
Vascular or ischemic pathology	• Vascular or ischemic pathology • Congested villi • Villous hemorrhage (intravillous) • Villous infarction (gross and microscopic) • Intervillous thrombus • Decidual vasculopathy • Decidual hemorrhage • Abruption • Fetal surface vessel/umbilical vessel thrombosis
Inflammatory pathology	• Villitis (villitis of unknown etiology)
Villous maturation disorder	• Delayed / Advanced • Dysmaturity / Variable • Chorioangiosis
Other isolated abnormalities	• Isolated membrane abnormality • Amnion nodosum / Meconium deposition • Isolated cord edema/ Isolated villous edem • Mild peri villous fibrin deposition

Neonatal Outcome and Placental Pathology

Our finding of an almost 20-fold increase in the odds of dying when amnion nodosum is present is more strongly predictive than extreme prematurity in our population. Amnion nodosum tends to be associated with oligohydramnios arising from various causes[50]; oligohydramnios itself can be a presenting feature of placental insufficiency. Whether oligohydramnios was a presenting feature in those infants whose placenta exhibited amnion nodosum is not known for our population. The significant correlation of villous edema with neonatal complications such as death, CLD, and IVH concurs with the findings of Redline et al.,[59] who found that grade 3 villous edema was associated with long-term neurological impairment in low birth weight neonates (OR 5.7;95% CI, 1.5–21.0). Villous edema, which has been linked to placental ischemia on the fetal side [60], is probably associated with impaired placental function, as emphasized by its correlation with IUGR in our population. Finally, placental maturity disorders were associated with both the presence of maternal hypertension and increased odds of neonatal death and of contracting nosocomial infections.

Chorangiosis, which has been associated with hypoxic insults to the placenta and adverse neonatal outcome by others[61], was not associated with IUGR or adverse outcome in our population. However, this pathology was associated with the presence of maternal hypertension. Christiane Krebs[62] in 1996 found that the terminal villous compartment of the placenta appears to be maldeveloped in preterm IUGR where absent diastolic flow is demonstrated in the umbilical artery before delivery. These findings are consistent with an increase in fetoplacental vascular impedence at the capillary level and may account for the impaired gas and nutrient transfer in this disorder.



AIM OF THE STUDY

The placental villous dysfunction in growth restricted foetuses with abnormal umbilical artery blood flow is characterised by reduced elaboration of gas-exchanging peripheral villi, which increase the risk of chronic fetal hypoxia and acidosis.

Histologic examination of the placentas from IUGR fetuses can supplement clinical knowledge of the cause of IUGR. The knowledge about placental histopathology and its maternal and fetal implications are lacking and very few studies have examined the correlation between Doppler findings and placental pathology. As with many maternal and fetal conditions, careful evaluation of the placenta may aid in diagnosis of an underlying condition, a recurrent condition, chromosomal abnormalities, or systemic diseases.

The present study was undertaken to analyse the umbilical artery Doppler velocity waveforms in pregnancies complicated by intrauterine growth restriction and to correlate it with the histopathology of the placenta.

MATERIALS AND METHODS

STUDY DESIGN:

Prospective observational study

SOURCE OF DATA:

This study was carried out in the antenatal cases who were booked and delivered, at the Department of Obstetrics and Gynaecology, PSG Hospitals, Coimbatore. 64 cases were enrolled during the study period from April 2008 to September 2009.

INCLUSION CRITERIA:

Singleton pregnancies complicated by IUGR identified antenatally according to following criteria: clinical screening / serial screening of growth - which includes symphysio-fundal height & abdominal palpation (fundal height which is lacking by 4 or more weeks are included) and ultrasonographic disparity in AC >2 weeks were included in the study.

EXCLUSION CRITERIA:

1. Twin pregnancies
2. No ultrasonogram before 24 wks of gestation to confirm the gestational age
3. Known congenital anomaly in the fetus.

METHOD OF COLLECTION OF DATA:

In this study, antenatal cases with pregnancies complicated by IUGR were identified and who fulfilled the criteria mentioned above were enrolled as cases. For

each case, history as mentioned in the structured proforma was taken followed by a general, physical, systemic and obstetric examination.

Ultrasonogram was done in the cases and following parameters including fetal biometry, estimated fetal weight, amniotic fluid index, and doppler ultrasound of the umbilical artery were noted. The umbilical artery waveform was measured from a free- floating loop of cord during fetal quiescence. The last value measured within 48 hrs before delivery in all cases was used for this study. Based on Doppler findings the cases were categorised as with normal diastolic flow or reduced / absent / reversed end diastolic flow.

Immediately after delivery, the newborn is weighed and the birth weight percentiles were determined by previously published normal curves by Alexander GR in 1996[63]. The placentas were weighed and sent to the Department of Pathology where gross and histopathological examination was done by a senior pathologist.

Placental histologic data examined include decidual vasculopathy, retroplacental hematoma, fetal thrombotic arteriopathy, chorangiosis, acute inflammation,chronic deciduitis, intervillous thrombus and microcalcification. Based on the placental histologic findings the placental pathology was subclassified and grouped as shown in table below proposed by Beebe et al[52]. The placental pathology thus identified was used for analysis and correlated with respective umbilical artery Doppler findings.

Table 8

Fetal weight percentiles throughout Pregnancy

Alexander G.R et al., [63]

I Gestational age (weeks)	5th Percentile	10th Percentile	50th Percentile	90th Percentile	95th Percentile
20	249	275	412	772	912
21	280	314	423	790	957
22	330	376	496	826	1023
23	385	440	582	882	1107
24	435	498	674	977	1223
25	480	558	779	1138	1397
26	529	625	899	1362	1640
27	591	702	1035	1635	1927
28	670	798	1196	1977	2237
29	772	925	1394	2361	2553
30	910	1085	1637	2710	2847
31	1088	1278	1918	2986	3108
32	1294	1495	2203	3200	3338
33	1513	1725	2458	3370	3536
34	1735	1950	2667	3502	3697
35	1950	2159	2831	3596	3812
36	2156	2354	2974	3668	3888
37	2357	2541	3777	3755	3956
38	2543	2714	3263	3867	4027
39	2685	2852	3400	3980	4107
40	2761	2929	3495	4060	4185
41	2777	2948	3527	4094	4217
42	2764	2935	3522	4098	4213
43	2741	2907	3505	4096	4178
44	2724	2885	3491	4096	4122

Table 9

Subclassification of Placental pathologies in IUGR (Beebe et al.,[52])

Subclassification	Placental findings
Vascular or ischemic pathology	• Vascular or ischemic pathology • Congested villi • Villous hemorrhage (intravillous)

	• Villous infarction (gross and microscopic) • Intervillous thrombus • Decidual vasculopathy • Decidual hemorrhage • Abruption • Fetal surface vessel/umbilical vessel thrombosis
Inflammatory pathology	• Villitis (villitis of unknown etiology)
Villous maturation disorder	• Delayed / Advanced • Dysmaturity / Variable • Chorioangiosis
Other isolated abnormalities	• Isolated membrane abnormality • Amnion nodosum / Meconium deposition • Isolated cord edema/ Isolated villous edem • Mild peri villous fibrin deposition

Method of Statistical Analysis:

The results for each parameter (numbers and percentages) for discrete data and averaged (mean + standard deviation) for continuous data are presented in Table and Figure. The Proportions were compared using Chi-square test of significance. In the above test the "p" value of less than 0.05 was accepted as indicating statistical significance. Data analysis was carried out using Statistical Package for Social Science 13 (SPSS) package.

RESULTS AND ANALYSIS

Total of 64 cases with IUGR were included in this study. The observations and results of the study are presented in the following pages.

DISTRIBUTION OF CASES BASED ON AGE:

As shown in the table, out of 64 cases the majority belong to 20-30yrs (81%) with the rest being in >30yrs (11%), and <20 yrs (8%) group.

Table 10

AGE	CASES	
	NUMBER	PERCENT
< 20 YRS	5	7.8%
20 – 30 YRS	52	81.3%
> 30 YRS	7	10.9%
TOTAL	64	100%

DISTRIBUTION OF CASES BASED ON GESTATIONAL AGE:

Out of 64 cases, 70% were preterm and 30% were term IUGR as depicted in the table below

Table 11

GESTATION	CASES	
	NUMBER	PERCENT
Preterm	45	70.3%
Term	19	29.7%
Total	64	100%

DISTRIBUTION OF CASES BASED ON ETIOLOGY:

As shown in the table, out of 64 cases, the major etiology for IUGR were PIH and idiopathic which accounted for 42% each. Other etiologies include Cardiac disease complicating pregnancy (6%) and miscellaneous (10%).

The miscellaneous group comprised the following etiologies: Connective tissue disorder (3), Diabetes mellitus (1), uterine malformations (1), bronchial asthma(1).

Table 12

ETIOLOGY	CASES	
	NUMBER	PERCENT
Idiopathic	27	42.2%
PIH	27	42.2%
Cardiac	4	6.3%
Miscellaneous	6	9.4%
Total	64	100%

DISTRIBUTION OF OLIGOHYDRAMNIOS AMONG CASES:

Oligohydramnios (<8 cms) was present in 67% of the cases as shown in the table below. Among 43 cases with oligohydramnios, 19 had AFI of less than 5 cm.

Table 13

OLIGOHYDRAMNIOS	CASES	
	NUMBER	PERCENT
Present	43	67.2%
Absent	21	32.8%
Total	64	100%

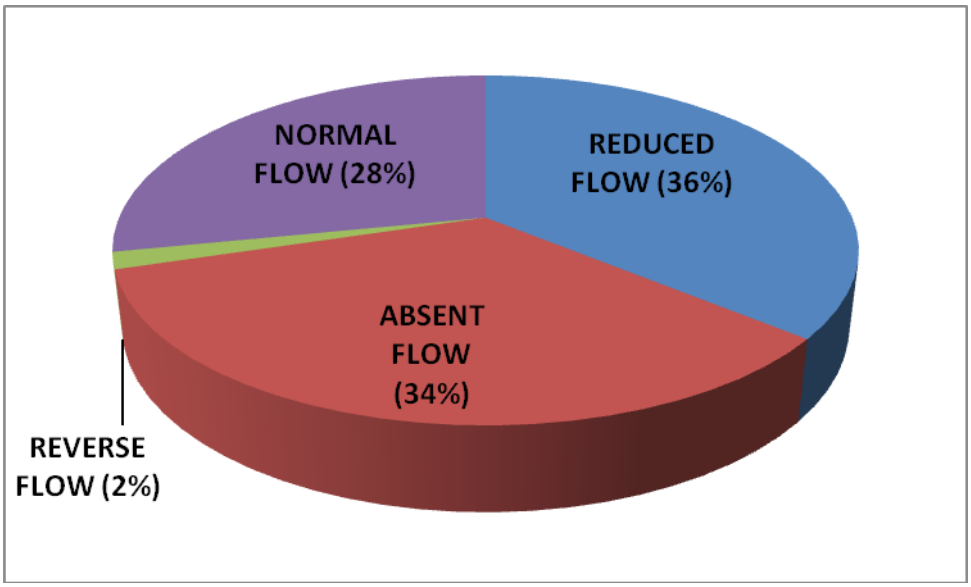
DISTRIBUTION OF UMBILICAL ARTERY DOPPLER WAVEFORMS IN CASES:

As shown in the table and pie chart, out of 64 cases, reduced end diastolic flow was seen in 36%, absent end diastolic flow in 34% and reversed flow in 2%. Normal end diastolic flow was present in the rest 28%.

Table 14

UMBILICAL ARTERY DOPPLER CHANGES	CASES	
	NUMBER	PERCENT
Reduced diastolic flow	23	35.9%
Absent diastolic flow	22	34.4%
Reverse diastolic flow	1	1.6%
Normal flow	18	28.1%
Total	64	100%

Fig 8: Distribution of Umbilical Artery Doppler Waveforms



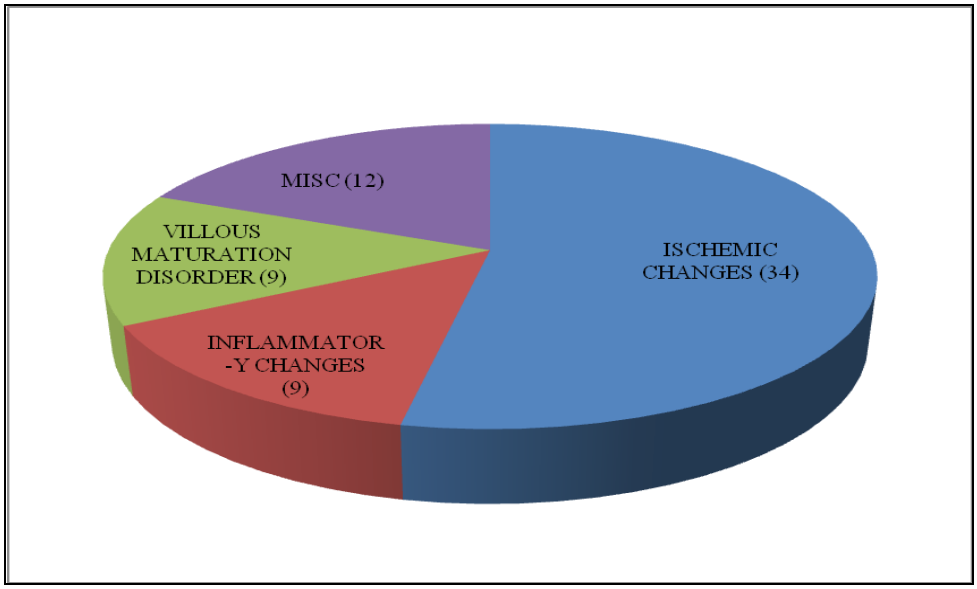
DISTRIBUTION OF PLACENTAL PATHOLOGY IN CASES:

Among 64 cases, 34 (53.1%) cases had ischemic pathology, 9 (14.1%) had inflammatory, 9 (14.1%) had villous maturation disorder and 12 (18.8%) cases had miscellaneous placental changes like mild perivillous fibrin.

Table 15

PLACENTAL PATHOLOGY	CASES	
	NUMBER	PERCENT
Ischemic changes	34	53.1%
Inflammatory changes	9	14.1%
Villous maturation disorder	9	14.1%
Miscellaneous	12	18.8%
TOTAL	64	100%

Fig 9: Placental Pathology



COMPARISON OF UMBILICAL ARTERY DOPPLER (NORMAL AND ABNORMAL) WAVEFORMS WITH PLACENTAL PATHOLOGY:

Out of 64 cases, 46 cases had abnormal Doppler waveforms (reduced, absert and reversed diastolic flow). Among this 46 cases, 28 (60.8%) cases had ischemic placental pathology, 8 (17.4%) cases had inflammatory pathology, 7 (15.2%) had maturation disorder and 3 (6.5%) had miscellaneous placental changes like mild perivillous fibrin deposition.

In the remaining 18 cases who had normal Doppler flow, 6 (33.3%) cases had ischemic placental pathology, 1 (5.5%) had inflammatory pathology, 2 (11%) had maturation disorder and 9 (50%) had miscellaneous placental changes like mild perivillous fibrin deposition.

Ischemic, inflammatory and villous maturation disorder placental pathologies were more commonly observed in cases with abnormal doppler waveforms when compared with normal doppler waveforms with difference being statistically significant with $p < 0.005$.

Table 16

DOPPLER	PLACENTAL PATHOLOGY				TOTAL
	ISCHEMIC	INFLAMMATORY	VILLOUS MATURATION DISORDER	MISC	
Abnormal flow	28 (60.8%)	8 (17.4%)	7 (15.2%)	3 (6.5%)	46 (100%)
Normal flow	6 (33.3%)	1 (5.5%)	2 (11%)	9 (50%)	18 (100%)
Total	34 (53%)	9 (14.1%)	9 (14.1%)	12 (18.8%)	64 (100%)

Statistics	DF	Value	Probability
Chi-Square	3	16.33	0.001

COMPARISON OF ABNORMAL UMBILICAL ARTERY DOPPLER WAVEFORMS WITH PLACENTAL PATHOLOGY:

Among 23 cases with reduced diastolic flow, majority (39.1%) had ischemic pathology, inflammatory, villous maturation disorder pathology accounting for 26% and 21.7% respectively and miscellaneous changes accounts for 13%. Similarly, ischemic pathology was the most predominant placental pathology in absent diastolic flow(81.8%) and reverse diastolic flow (100%).

In contrast, the normal Doppler waveform was more commonly associated with miscellaneous placental changes (50%) rather than ischemic changes.

The difference between these groups was statistically significant with p <0.005.

Table 17

DOPPLER	PLACENTAL PATHOLOGY				TOTAL
	ISCHEMIC	INFLAMM-ATORY	VILLOUS MATURATION DISORDER	MISC	
Reduced flow	9 (39.1%)	6 (26%)	5 (21.7%)	3 (13%)	23 (100%)
Absent flow	18 (81.8%)	2 (9%)	2(9%)	0 (0%)	22 (100%)
Reverse flow	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
Normal flow	6 (33.3%)	1 (5.5%)	2 (11%)	9 (50%)	18 (100%)
Total	34 (53%)	9 (14.1%)	9 (14.1%)	12 (18.8%)	64 (100%)

Statistics	DF	Value	Probability
Chi-Square	9	25.5	0.002

Fig 10: Bar diagram showing placental pathology and umbilical artery doppler waveforms (X axis – doppler flow; Y axis – placental HPE changes

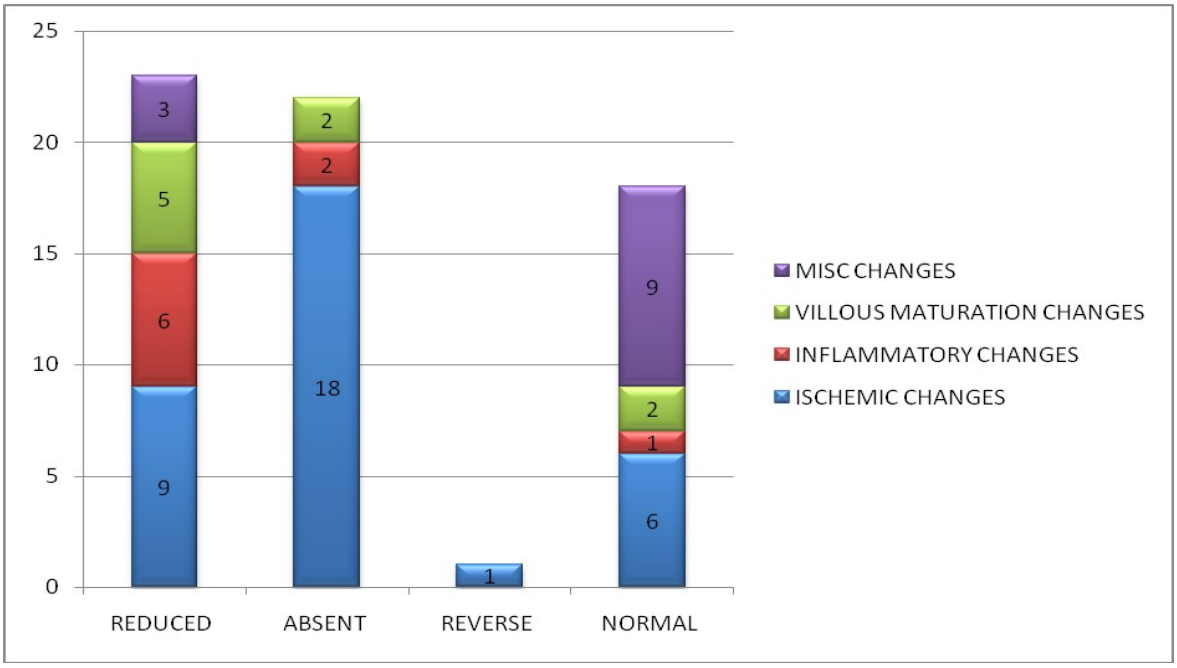


Fig 11 : Normal umblical artery wave forms

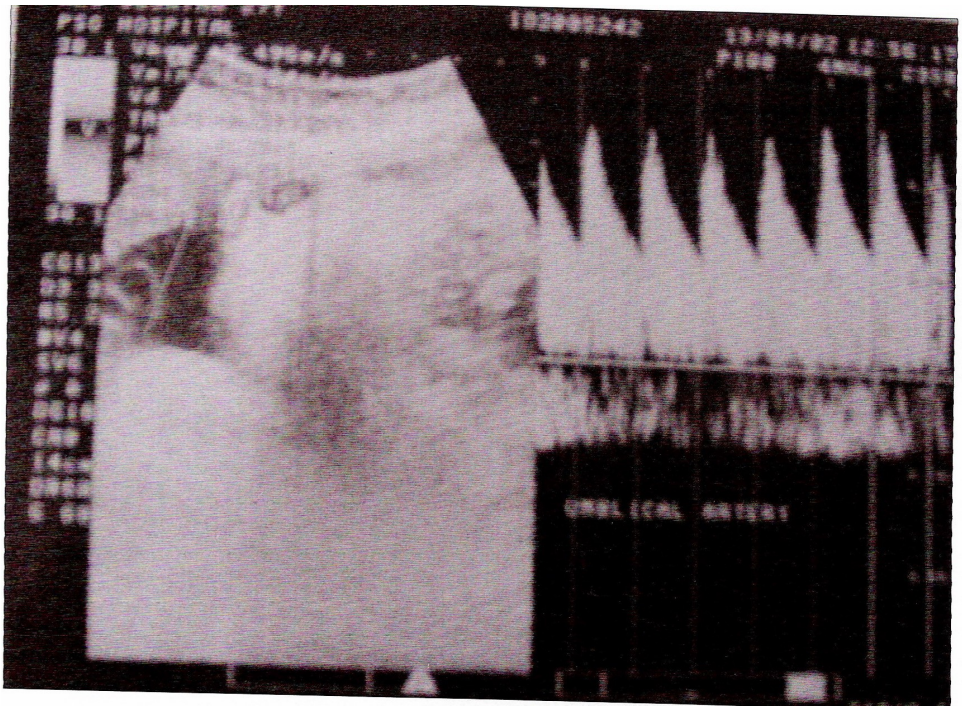


Fig 12: Reduced diastolic artery wave froms of the umblical artery

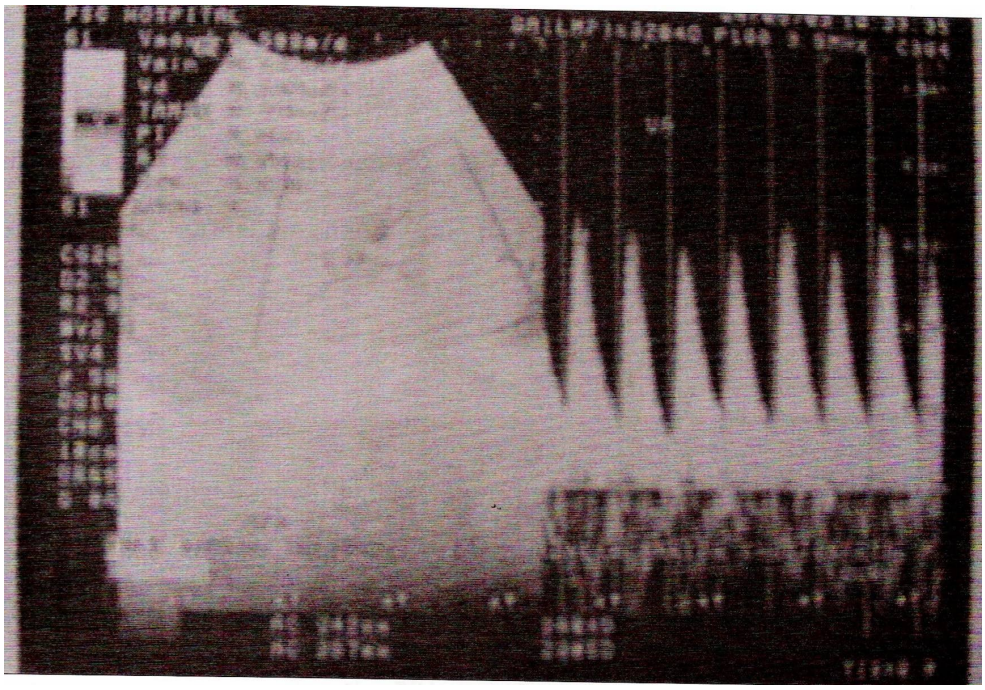


Fig 13 : Gross examination of placenta showing solid yellow areas of infarction

Fig 16 : Microscopic placental examination shows villitis of unknown etiology – the villi shows an inflammatory infiltrate and some of them are necrotic (10X)

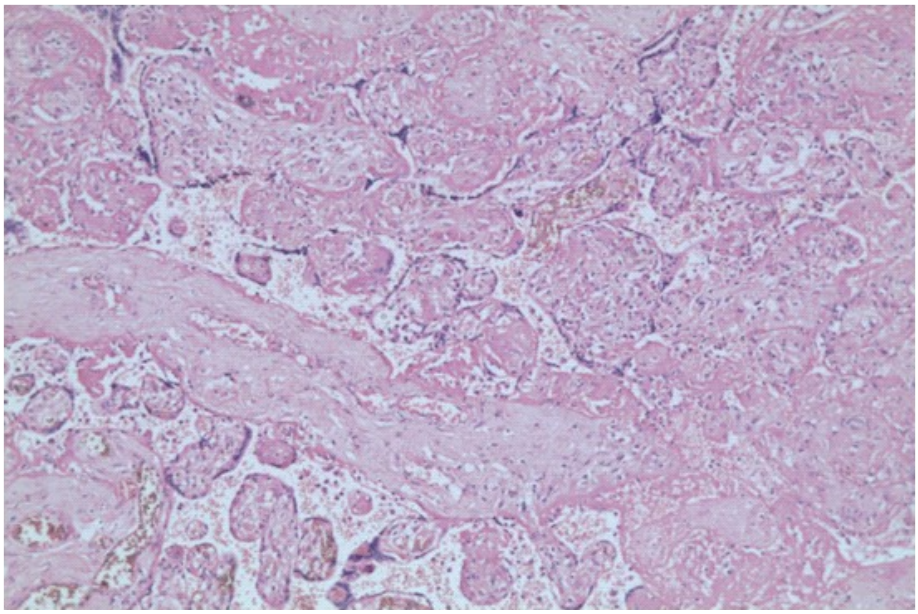


Fig 16 : High power view of the same placenta shows villitis of unknown etiology – there is prominent lymphocytic infiltrate in a villous. (40X)

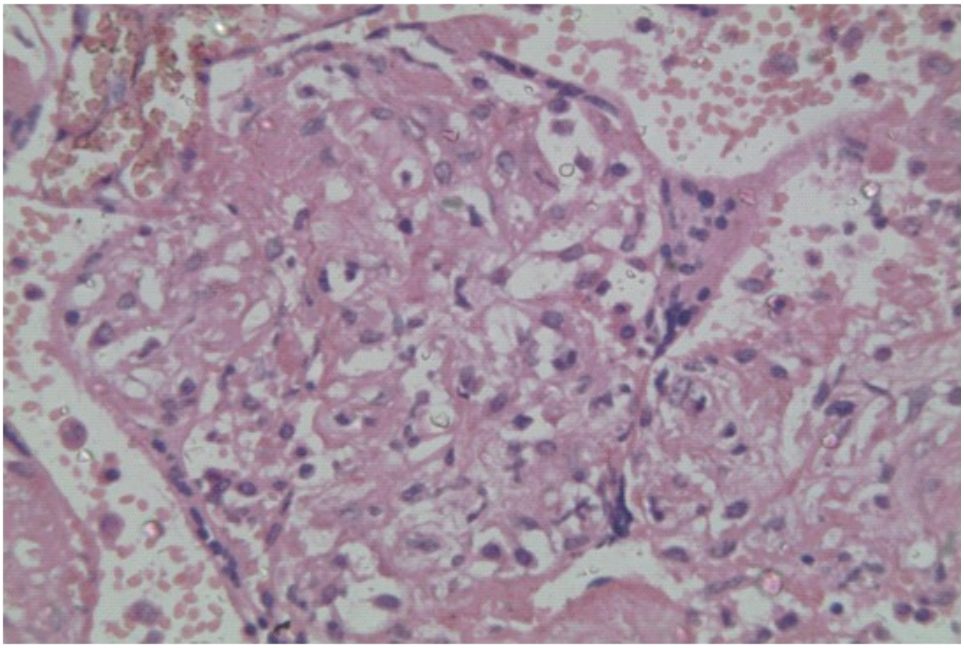


Fig 17: Decidual vasculopathy-fibrinoid necrosis and foam cells (atherosis) in decidual arterioles.

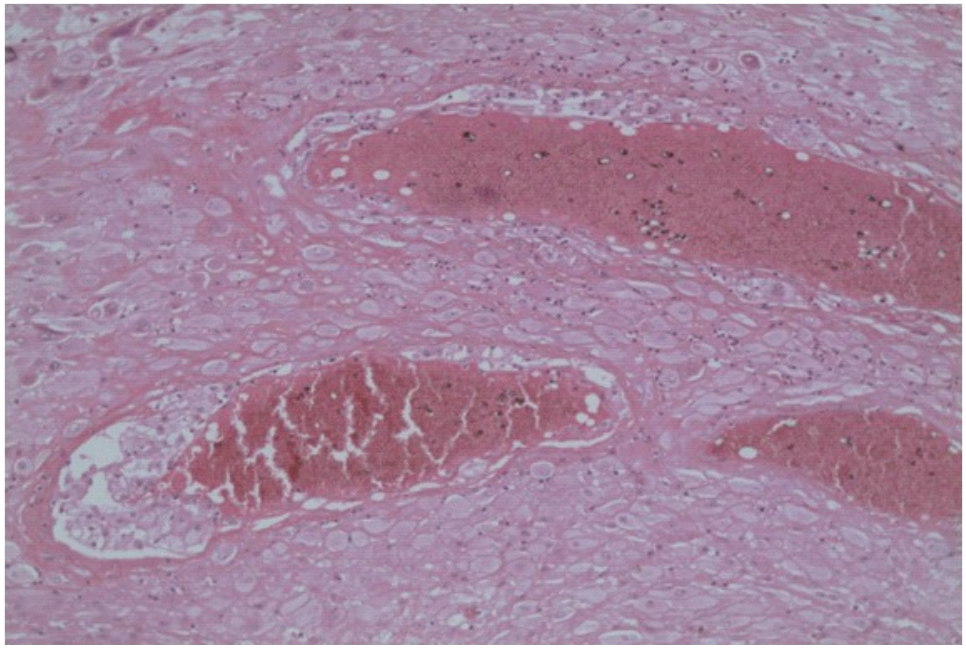


Fig 18: Decidual vasculopathy – spiral arterioles in the decidua have a thick muscular wall.

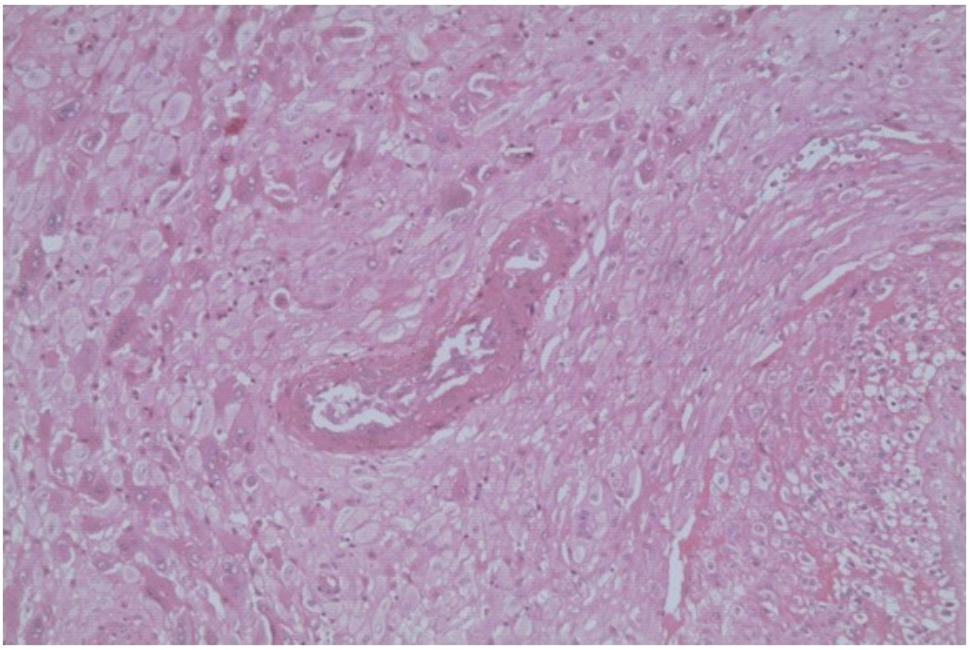


Fig 19: Infarct – there is coagulation necrosis of villi

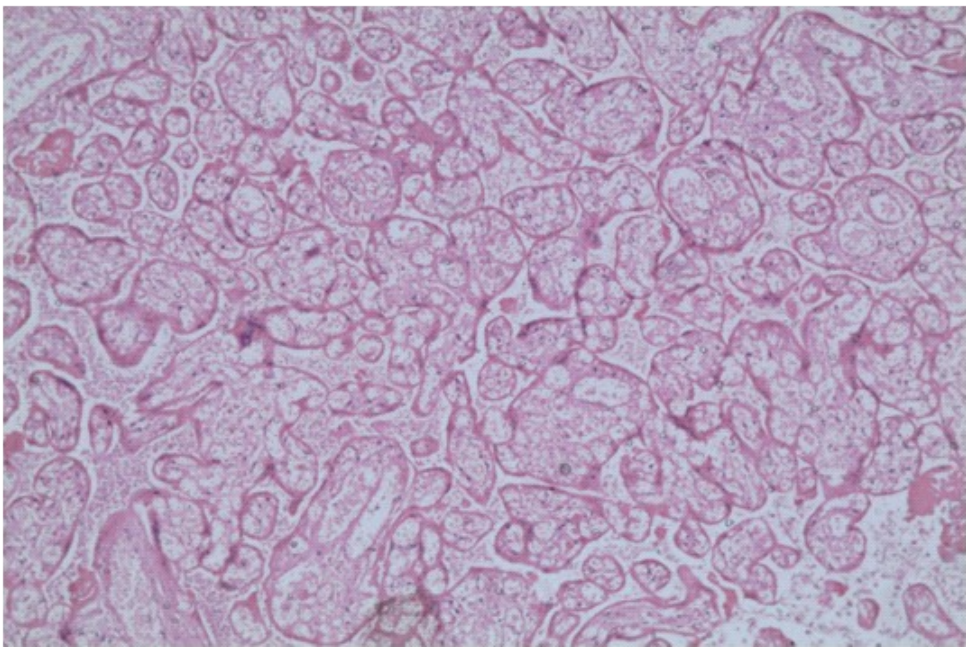


Fig 19: Villous hypoplasia -the terminal villi are of narrow caliber and filiform. The intervillous space appears to be expanded.

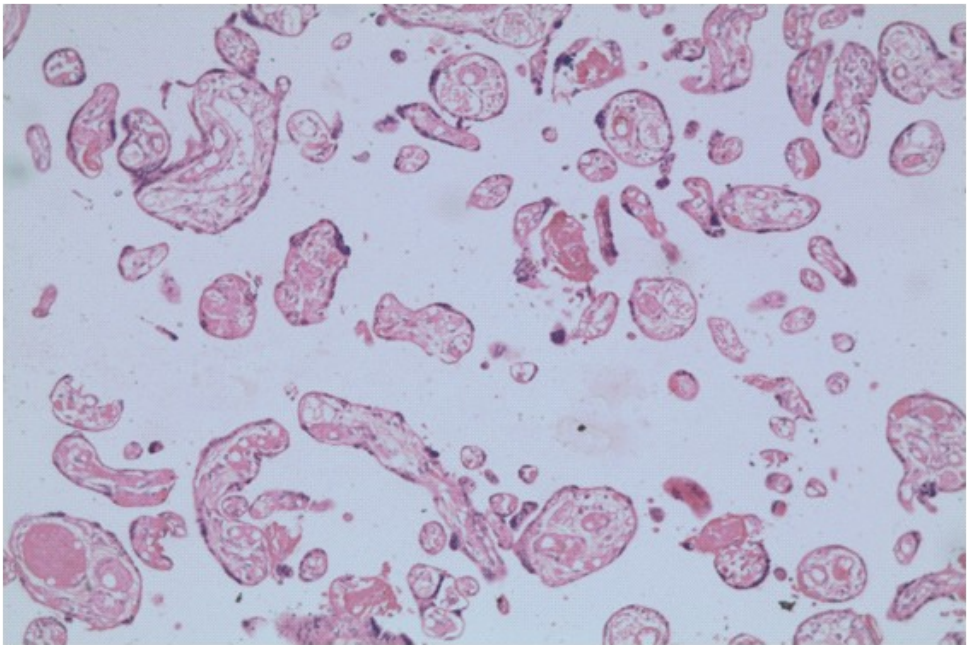
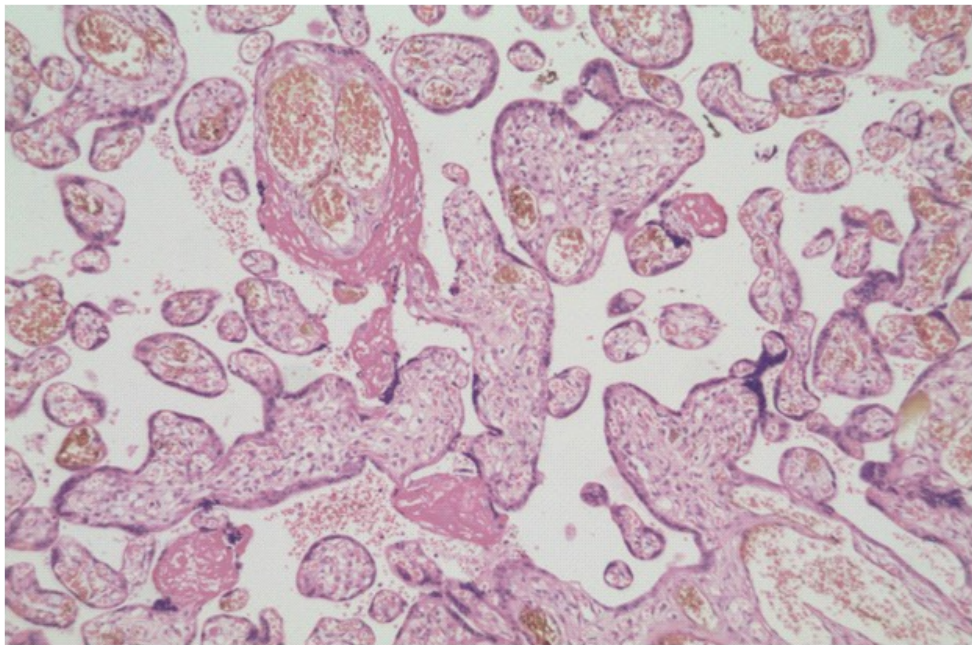
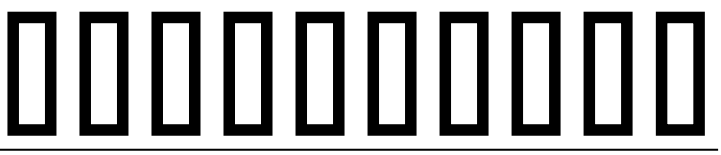


Fig:20 Villous immaturity-the villi in this placenta are large with a reticular stroma and are covered by a layer of syncytiotrophoblast. Syncytiovascular membranes are not well formed.





DISCUSSION

Intrauterine growth restriction is a major obstetric problem and is associated with high perinatal morbidity and mortality. Doppler assessment of the umbilical arterial circulation is an established test of fetal well being in pregnancy with IUGR. Assessment of placental pathology is an invaluable tool in determining the pathophysiology behind the growth restriction. It is also useful for determining the underlying mechanisms leading to pregnancy complications and for guiding future investigations and interventions relating to pre-pregnancy counselling and pregnancy care.

It is generally accepted that intrauterine events have an important effect on neonatal mortality and the development of long-term morbidity. Therefore, placental examination may represent a means of investigating the intrauterine past to explain the present condition of the neonate. Timely examination of the placenta may even help in guiding therapies or surveillance of infants deemed at increased risk for mortality or significant morbidity. The results of this study provide new evidence for the relationship between intrauterine events, reduced fetal growth velocity, and postnatal consequences. Specific patterns of placental pathological findings may be predictive of specific adverse neonatal outcomes.

In this study antenatal cases with pregnancies complicated by IUGR were identified. For each case, ultrasonogram was done in the cases and following parameters including fetal biometry, estimated fetal weight, amniotic fluid index, and Doppler ultrasound of the umbilical artery were noted. Based on Doppler findings the cases were categorised as with normal diastolic flow or reduced / absent / reversed end diastolic flow. The placentas were weighed and sent for histopathological

examination. Based on the placental histologic findings the placental pathology was subclassified into ischemic, inflammatory, villous maturation placental pathology and miscellaneous placental changes like mild perivillous fibrin deposition. The placental pathology thus identified was used for analysis and correlated with respective umbilical artery Doppler findings .

The observations of the study based on the chi square test reveal significant difference in the placental pathology in groups with abnormal doppler waveforms when compared with normal doppler waveforms with difference being statistically significant with $p < 0.005$. An attempt is made to discuss the main findings by comparing and contrasting with those of earlier studies and observations.

PLACENTAL PATHOLOGY IN CASES WITH ABNORMAL DOPPLER WAVEFORMS:

According to the present study, ischemic changes were the most common placental pathology accounting for 60.8% of cases with abnormal doppler waveforms. Inflammatory changes and villous maturation disorders were noted in 17.4% and 15.2% of cases respectively. Ischemic, inflammatory and villous maturation disorder placental pathologies were more commonly observed in cases with abnormal doppler waveforms when compared with normal doppler waveforms with difference being statistically significant with $p < 0.005$.

The study of Krebs et al[62] on 10 placentas of pregnancies with IUGR and absent diastolic flow in umbilical artery also illustrated that the terminal villous compartment of the placenta was maldeveloped with an increase in fetoplacental vascular impedance at the capillary level leading to ischemia and impaired gas and nutrient transfer in this disorder.

Luc Beaudet et al[64] in their study on 246 placentas of IUGR pregnancies found that changes associated with decreased placental perfusion such as ischemic changes were present in more than 70% of cases. These changes were more frequently seen in IUGR pregnancies with abnormalities in umbilical artery doppler measurements similar to findings of our study. Villous maturation abnormalities (18%) and inflammatory changes (12%) were also seen in these placentas as noted in our study.

Chie-Pein Chen et al[65] who examined the morphologic features of 9 placentas from pregnancies with severe intrauterine fetal growth restriction with abnormal umbilical artery blood flow velocity waveforms showed that peripheral villous vascularization was highly reduced suggestive of ischemic placental change compared with controls with normal umbilical artery doppler waveform.

Tullia Todros et al[40] examined 18 placentas with IUGR in which 10 had normal end diastolic flow and 8 had absent / reverse end diastolic flow. This study showed that placentas with absent / reverse end diastolic flow had terminal villous maldevelopment with ischemic changes consistent with the findings of our study.

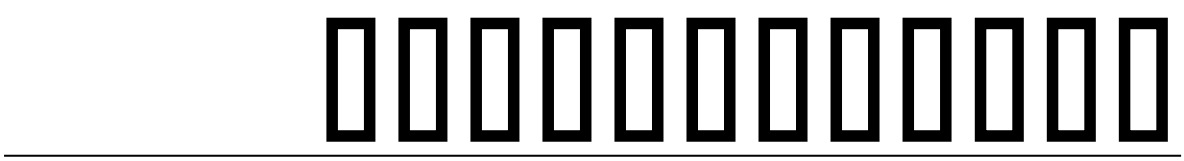
PLACENTA PATHOLOGY IN CASES WITH NORMAL DOPPLER:

In our study, cases with IUGR with normal Doppler waveforms were more commonly associated with miscellaneous placental changes like perivillous fibrin deposition.

Tullia Todros et al[40] showed that placentas with normal diastolic flow had changes similar to those observed in preeclampsia. This is suggestive of an adaptive pathway for the placenta like branching capillary angiogenesis which might have occurred in the face of uteroplacental ischemia to show normal end diastolic flow.

CONCLUSION

1. Histopathological examination of placenta in cases with IUGR revealed pathological changes like Ischemia, Inflammation and Villous maturation disorders.
2. Ischemic, inflammatory and villous maturation disorder placental pathologies were more commonly observed in cases with abnormal doppler waveforms when compared with normal doppler waveforms with difference being statistically significant with $p < 0.005$.
3. In cases with abnormal end diastolic flow the major associated placental pathology was ischemia more so with absent and reverses diastolic flow than reduced diastolic flow with difference being statistically significant with $p < 0.005$.
4. In cases with IUGR with normal end diastolic flow, majority were associated with miscellaneous placental changes like mild perivillous fibrin deposition which is of less significance.
5. It is well recognised that all institutions do not have pathologist with experience in doing placental pathology. If protocols are instituted such that placentas from all cases of IUGR are subjected to histopathological examination, it will allow a more complete understanding of the pathophysiology of fetal growth restriction, knowledge of risk of additional complications to the mother and the neonate, and the risk of recurrence in subsequent pregnancies.



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PROFORMA

" A correlation study between umbilical artery doppler wave forms and placental histopathology in pregnancies complicated by IUGR "

Name		**OP No**	
Age		**IP No:**	
Husband Name Address			
Occupation Religion:		Socio economical status	

Obstetric Score:

LMP : **Gestational age by LMP:**

EDD : **Gestational age by USG (before 24 weeks)**

Menstrual H/O:

Marital H/O:

Obstetrics H/O:

Past H/o:

Family H/o:

General Examination on admission:

Height Weight
Edema Pallor
PR BP

P/A: Symphysio fundal height

Abdominal girth

Risk factors:

Antenatal investigations

Hb				Blood Gr		HIV	
				VDRL			
Urine Re				GCT		HBsAg	

Others:

Ultrasound

Date			
GA by LMP			
GA by USG			
BPD			
FL			
AC			
AFI			
Doppler Um.A			
USG comments			

In labour:

- Term / Preterm
- Mode of delivery ☐ Vaginal ☐ Elective CS ☐ Emergency CS
  - If vaginal, ☐ Spontaneous ☐ Induced
  - If induced, mode of induction:
- Labour: ☐ Fetal distress ☐ Color of amniotic fluid
  ☐ Duration of labour:

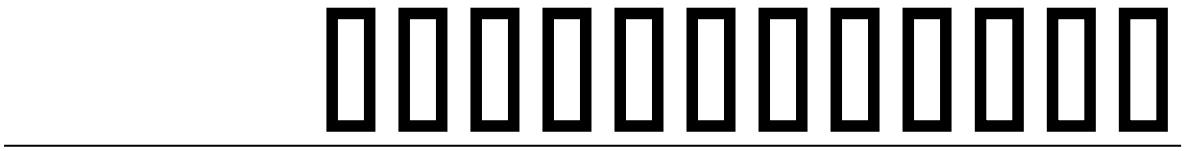
  I stage
  II stage
  III stage

Baby details:

- Condition at birth APGAR
- Birth weight Sex
- Placental weight NICU admission:
- Neonatal complications:

Maternal / postnatal complications, (if any)

Placental Histopathology report:



MASTER CHART

S.NO	IP. NO.	AGE	GRAVIDA	GESTATION	ETIOLOGY	OLIGOHYDRAMNIOS	DOPPLER	PLACENTAL CHANGES	MODE OF DELIVERY	CONDN AT BIRTH	BIRTH WEIGHT
1	I08045119	1	1	0	3	0	3	3	0	0	0
2	I08045312	2	0	0	1	0	1	0	0	0	0
3	I08045275	1	0	0	0	0	0	0	0	0	0
4	I08045763	1	0	0	2	0	3	3	0	0	1
5	I08046354	1	0	0	0	1	0	1	0	0	0
6	I08046362	1	1	0	0	0	3	0	0	0	0
7	I08047140	1	0	0	1	0	0	1	0	0	0
8	I08047206	1	0	0	0	0	0	1	0	0	0
9	I08047797	0	0	0	0	0	3	0	2	0	0
10	I08048090	0	0	0	0	1	3	1	0	0	0
11	I08048704	1	0	1	0	0	3	3	0	0	0
12	I08048507	1	0	0	1	1	1	0	0	0	0
13	I08049297	2	1	1	0	0	3	3	0	0	0
14	I08049520	1	0	1	0	1	0	0	0	0	1
15	I08048227	1	1	0	2	1	1	0	0	1	0
16	I08050084	1	1	0	1	0	3	0	0	0	0
17	I08050027	1	1	1	0	1	1	2	0	0	0
18	I08049912	1	0	1	0	1	0	3	1	0	1
19	I09000141	1	0	0	3	0	0	0	2	0	1
20	I09001561	1	1	0	0	0	3	0	0	0	0
21	I09001815	1	0	0	2	0	3	3	1	0	0
22	I09001806	1	0	0	1	1	0	0	2	0	0
23	I09002725	1	1	0	1	0	1	0	2	0	0
24	I09094143	1	0	0	1	1	3	0	0	1	0
25	I09002760	2	1	0	1	0	3	0	0	0	0
26	I09005326	1	1	0	0	1	1	0	0	0	0
27	I09005894	1	1	0	1	0	1	0	1	0	0
S.NO	**IP. NO.**	**AGE**	**GRAVIDA**	**GESTATION**	**ETIOLOGY**	**OLIGOHYDRAMNIOS**	**DOPPLER**	**PLACENTAL CHANGES**	**MODE OF DELIVERY**	**CONDN AT BIRTH**	**BIRTH WEIGHT**
28	I09008567	1	0	1	3	1	1	0	0	0	0
29	I09008725	1	0	0	1	1	1	0	0	1	0

30	I09008141	1	0	0	1	0	1	0	2	0	0
31	I09009742	0	0	1	0	0	3	2	2	0	0
32	I09012449	1	0	1	1	0	3	2	2	0	0
33	I09014691	1	1	0	1	0	1	0	2	0	0
34	I09015128	1	0	1	0	1	3	3	0	0	0
35	I09015473	1	0	0	0	0	3	3	2	0	0
36	I09017858	2	1	0	3	0	0	0	2	0	0
37	I09018653	1	1	1	1	1	1	0	0	0	0
38	I09020659	1	1	0	1	0	3	3	2	0	0
39	I09020951	1	1	1	0	1	0	3	2	0	0
40	I09021715	1	0	1	0	0	1	0	0	0	0
41	I09022612	0	0	0	1	0	2	0	0	0	0
42	I09022750	1	0	0	1	1	1	0	0	0	0
43	I09023496	1	1	0	1	1	0	0	2	0	0
44	I09023981	1	1	0	0	1	0	1	0	0	0
45	I09023986	1	0	0	1	0	1	0	0	0	0
46	I09027014	2	1	0	3	0	1	2	2	0	0
47	I09027736	1	1	1	2	0	0	2	2	0	0
48	I09027803	1	1	0	1	0	0	0	0	0	0
49	I09027913	1	0	1	0	1	0	0	0	0	0
50	I09027976	1	0	0	3	1	0	3	0	0	0
51	I09029468	1	0	1	0	0	3	3	2	0	0
52	I09030527	1	0	0	1	0	1	0	0	0	0
53	I09032972	1	1	0	1	0	1	0	2	0	0
54	I09032686	1	1	0	1	0	1	1	2	0	0
55	I09033663	1	0	0	1	1	1	1	2	0	0
56	I09036871	2	1	0	1	0	0	0	2	0	0

S.NO	IP. NO.	AGE	GRAVIDA	GESTATION	ETIOLOGY	OLIGOHYDRAMNIOS	DOPPLER	PLACENTAL CHANGES	MODE OF DELIVERY	CONDN AT BIRTH	BIRTH WEIGHT
57	I09038996	1	0	1	0	0	0	2	2	0	0
58	I09038664	1	0	0	1	0	1	0	0	0	0
59	I09038996	1	0	1	0	0	0	2	2	0	0
60	I09038554	1	1	0	0	0	0	2	2	0	0
61	I09038938	0	0	0	0	0	0	1	2	0	0
62	I09040108	2	1	1	0	0	0	1	2	0	0
63	I09042064	1	1	0	1	0	1	0	2	0	0
64	I09045890	1	1	1	0	0	0	2	2	0	0

Key to master chart :

- 1. Age 0- <20 years, 1-20 years to 30 years, 2- >30 years
- 2. Gravida 0- Primi 1-Multi
- 3. Gestation 0- Preterm 1-term
- 4. Etiology 0- Idiopathic 1-PIH, 2- Cardiac, 3- Misc
- 5. Oligohydramnios 0- Yes 1-No
- 6. Oligohydramnios 0- Yes 1-No
- 7. Doppler 0- Reduced flow 1-absent flow, 2-reversed flow, 3- Normal
- 8. Placental Changes 0- ischemia 1-inflammatory, 2-villous maturation disorder, 3- Misc
- 9. Mode of Delivery 0- Normal 1-Assisted, 2-LSCS
- 10. Condition at birth 0- Live 1-Still birth
- 11. Birth Weight 0 <10^{th} percentile, 1-10th to 25^{th} percentile